I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Mail Stop: Petition to the PTO commissioner Objections on procedural matters
Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313-1450 on March 11, 2009

Applicant (Peter Migaly, M.D.)

March 11, 2009
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of	:	COMBINATION THERAPY FOR DEPRESSION, PREVENTION OF SUICIDE, AND VARIOUS MEDICAL AND PSYCHIATRIC CONDITIONS
Peter Migaly	:	
Application Serial Number 10/627,358	:	pro se (no layer) case
Filing Date: July 23, 2003	:	former ~~Docket Number: 290194-00001~~
Examiner: Eric Olson	:	Art Unit 1614

Objections on procedural matters, petition to the PTO commissioner to overrule a subordinate. and AMENDMENT AND RESPONSE

March 11, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This response starts with **Objections on procedural matters - petition to the PTO commissioner to overrule a subordinate - with** verified showing (declaration) **and also includes amendment and response.**

In response to the Office Action Dated September 12, 2008, please amend the above-identified application as follows:

03/16/2009 CNGUYEN2 00000007 10627358
02 FC:2201 220.00 OP
03 FC:2252 78.00 OP

A request of three months extension of time accompanies this response.

Petition to the PTO commissioner to overrule a subordinate - Objections on procedural matters on 34 different patterns. (The examiners have repeated these patterns almost countless of times). Please note the seriousness of the matter, and a verified showing (declaration) is also enclosed. (This begin on **page 3** of this paper).

Response and amendment to the 4th Office Action (OA) **and** the **line by line reply** starts at around **page 23.**

Summary points (in addition to and as part of the repy) to point out differences in prior art. This includes new references embedded in the text. This is also an attempt to help the reviewer for not to be lost in the vast number of prior communications. (begins on **page 153)**

Amendments to the Claims are reflected in the listing of claims which begins on **Page 192** of this paper.

Summary and Conclusions begin on **Page 219.**

Applicant also includes **enclosures**, and **attachments** (copies of selected professional publications referenced in the reply.

In addition, please note that the **Applicant has lost his attorney representation, is relying on your guidance**, and that his best (timely) contact is through his cell phone **(724)840-0464**
His address is Peter Migaly P. O. Box 237 Blairsville PA 15717

Objections on procedural matters
- petition to the PTO commissioner to overrule a subordinate.

Objections on procedural matters on 34 different patterns (patterns that the examiners have repeated almost countless of times).

> From the book Patent it yourself by patent attorney David Pressman, Nolo, 2004 p. 13/50-51:
> "If the examiner has made objections that [the applicant] thinks is wrong or if [the applicant] thinks [the applicant] has been treated unfairly or illegally, [the applicant] can petition the Commissioner to overrule a subordinate."

Declaration (for objections on procedural matters (pages 3-22):
I hereby declare that all statements made herein of my own knowledge, and to my best recollection, and to my opinion, and to my professional opinion, and to my discoveries and facts presented herein are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Peter Migaly, M.D. March 11, 2009

1) The PTO examiners have given evidence that they **have not read the applicant's submitted applications and replies in full**, and therefore have made judgments being repeatedly unaware of relevant information within the applications and replies. Multiple examples to this repeated deficiency is provided herein:

[Theory, existence of enablement and guidance was presented but the PTO examiners were not aware of them. The same is true for the secondary factors that the examiners did not take a notice. The examiners continued with their unconvincing reasoning that the effect of the invention could be explained and obvious by "faster antidepressant action" with the combination therapy when evidence to the contrary was previously presented (**4th OA, and see line by line reply below; Reply to the 1st OA p. 59, reply-22, see nalso utility p.14 lines 7-9, 22-26; see for guidance and theory e.g. Reply to the 1st OA p. p. 47 reply-6, p.51.**). The PTO was also not aware that the applicant has cited relevant PTO rules of why the rejection must be withdrawn **(e.g. reply to the 2nd OA p. 15, 20, 26, 27; or reply to the 3rd OA page 40-41).]**

Example provided under **#9** and also under **#5/C** below is further evidence that the examiners have not read the applicant's reply.

Further example is **reply to 3rd OA (pages 18 & 25)** on why Chappell is not enabling and why the PTO examiners did not have a convincing line of reasoning on Chappell's anticipating and making our claims obvious by mere mentioning of D4 receptor antagonist. The 4th OA did not reflect on the applicant arguments.

Please also see #II at p.54; #XiX p. 95 below.

Please also see (e.g.: page 9 lines 9-11 of the 4th OA: It seems that the examiners did not read our reply and our application, as our theory, guidance and enablement were specifically spelled out. E.g.: We have described of how the effect on the extended depressive symptoms would increase the effect of certain antidepressant symptoms and described a symbiotic action.
The effect on cognitive distortion is another factor and no prior art described that effect for antipsychotics. The PTO examiners reasoning to make this conclusion obvious were not convincing, and they failed to provide any prior art teaching the same. – see more on this later).

The last example under **8g/B** also supports that the PTO examiners did not read, and did are ignoring the applicant's reply.

Another example is that while the Robertson reference was included in the utility, the examiners started an objection about this only in a later OA. [The unconvincing nature of their reasoning and that the same argument was not brought up for other issued US patent is discussed elsewhere]. See #VIII p. 72 below.

2) The examiners have shown that while it is implied that they are taking an expert role in making decisions on the merit of the application, **they are in fact showing gross deficiencies in their knowledge of the field** that is exemplified by that they are not familiar with the basic and rudimentary principles of clinical decision making that is essential for clinical work and to avoid medical malpractice. The examiners are making judgment on what would be obvious to them now if clinical decision making and rules guiding and bounding to the person skilled in the art would be repeatedly ignored. Additional examples show that the examiners are not familiar with how
- divergent clinical guidelines, and
- strong teaching against,
- lack of enablement in prior art, and
- others inability to use our method (also as secondary factors) play a role in what would be considered by the skilled in the art "obvious" at the time of the invention. The examiners have made an office action without showing knowledge of the existence of how off label use of already approved medications can be used. The examiners have also shown that they do not fully grasp of how the risk/benefit and alternative analysis is essential in the clinical decision making and in deciding of what is "obvious", and of how the risk/benefit and alternative analysis can change with time and with new information revealed (e.g. by the applicant's guidance). Also the examiners have shown that they do not fully grasp of how that applies to enablement or lack of enablement of a method that has a strong teaching against, and thus just vague mentioning of two compounds to be used together for "all mental illnesses", or for a wide group of diagnostic category but without sufficient enablement and without any or without sufficient guidance in the prior art for a specific subgroup of patients that is not even explicitly disclosed would and could not make it obvious to use against said strong teaching against (e.g. as initial treatment). Thus no obviousness can possibly exist by the cited prior art which is not enabling. Secondary factors also support that statement.
The examiners are obviously not clinicians, but their repeated lack of pertinent knowledge coupled with the presented evidence that they have not fully read and familiarized themselves with the applicants submitted applications and replies, has made the applicant frustrated and feeling unfairly treated, as if a plumber would make decision on the merit of a vascular surgeon's invention, and of what is doable and what is not in the human body.

Additional example: Although the reply to the 3rd OA was just revisiting the issue of anxiety, depression and cognitive distortion are not interchangeable, (and [e.g. 4th OA p.13, lines 11-12] the PTO's statement is incorrect "of anxiety is reasonable considered to be a cognitive distortion" – as it is not considered one. The reasons discussed e.g. reply to the 3rdOA p.20, III2b) and p 18-21) were ignored by the PTO.. The PTO disregards all of the applicant's reply without even engaging of mentioning the counter-arguments and the PTO keeps copying over and over the same statement (e.g. p.13 lines 12-15 in the 4th OA. - compared to reply to the 3rd OA p. 18-21 III2a-III2f). The PTO's unconvincing reasoning (e.g. lines 6-8 in p 38 of 4th OA) and mere statement is clinically not a relevant answer to any of the applicant's above mentioned replies.

See also 4the OA and line-by-line reply, #IV at p. 59; and #**XXIV** p. 105-107; and #**XXVI** p. 110; and XXX p. 114 below.

3) The PTO examiners have **repeatedly ignored cited PTO rules** that the applicant repeatedly listed in his replies that why the examiners must adhere to the cited PTO rules. The examiners have ignored these cited laws **not even commenting on their merits**. The applicant has drawn these PTO rules from self help books written by patent attorneys on how to craft the reply.

(E.g. bold fonts reply to the 1st OA pages 60, 68, 70, 75; reply to the 2nd OA pages 14-15, 17-18, 19, 20, 26, reply to the 3rd OA pages 23, 24 and 24 again, 26, 35-36, 41-42, 70).

4) The PTO examiners have **disregarded** applicant's detailed notes and attachments on applicable **secondary factors**, not taking them into consideration. In fact the examiners totally ignored the existence of the listed secondary factors and not till the very last reply were they making a mention downplaying them only to one of these factors. Examples for reference by page numbers and replies to office actions is given herein:

In the last OA (**p 49**.) the examiner finally – and for the first time - makes a comment on the secondary factor, and (in the applicant's view misapplying the reference incorrectly) the PTO is stating that "a rejection for anticipation under 35 USC 102(b) is a statutory bar and no secondary considerations can serve to overcome it". The problem is that **the alleged "anticipation" occurred only in the examiners' mind and not for the skilled in the art**. Thus the OA gave the false impression of said alleged "anticipation" existing that could only taken place due to the examiners' repeated unconvincing reasoning, and lack of understanding of how clinical decision making is governed, and how the clinical decisions are changed in one way or other again and again over time with new information, enablement and sufficient guidance becoming available. Thus what may be anticipated by a lay person in reading the applicant's writing is no assurance that it would have been anticipated by the skilled in the art without the knowledge of the applicant's guidance and revealing information. That guidance was removing certain obstacles. In fact this is what secondary factors also show. This is why there is a discrepancy between the examiner's lay thinking (with previously revealed lack of clinical skills) and the thinking of the skilled in the art as the secondary factors point this out. The examiner is still ignoring number of other secondary factors, and not even comments on the existence of them. **(See e.g.: relply to 1st OA p 93-94, relply to 2nd OA #II p. 32-34, In addition enclosed attachement/publications were also enclosed with the replies related to the secondary factors).**

On **page 47** of last office action the examiner brings up secondary factors again (but did not even make a mention of the cited secondary factors in any of the prior OAs). While in that part it is felt that the examiner's summary for the invention is grossly downplayed,

oversimplified and leaves out important parts and claims, it is pertinent for here that the examiners state that "a shift in priorities [from minimizing harm to maximizing benefit] is not patentable unless it results in an unexpected benefit". First of all the invention is not just about "shift in priorities". Second: Doesn't the achievement made possible by the applicants invention is an unexpected benefit (as stated in the **reply to the 3rd OA page 78**) of overcoming a long felt need unsolved by others and when the invention could have saved more lives then half the fatalities by the worst (contagious) infectious epidemics of all times in the USA (the fatalities of the 1918 flu – which asked for more lives then AIDS)???!!! Moreover, saving that many lives could have occurred approximately within the timeframe of the evaluation of this application, making the unexpected benefit even stronger!
Thus the examiners are making statements by not being aware of the information and facts presented in the applicant's replies.

5) The PTO examiners have **refused** – against the PTO regulation of the applicant's continued request for help from the PTO including and as needed for claim-drafting assistance **under MPEP 707.07(j).** Please note that since the submission of the utility the applicant has lost his attorney representation (his attorney has fired him for not limiting his reply to the attorney's summary [from pages 29-43 of the reply to the 1st OA] but wanting to include and including the facts and details following that part). Therefore, without attorney, the applicant was eligible to such mandated help by PTO examiners (that request was ignored and thus denied).

This even bears of enhanced importance as exemplified herein:
A) In the reply to the 2nd OA at page 40 the applicant has crafted and proposed some alternate claims and asked for the examiner's opinion on these claims if they would be acceptable to overcome the examiners' prior rejection. The examiners have not only not complied with the above PTO regulation, failing for providing claim drafting, but also ignored that part in the applicant's reply not even commenting on it in the subsequent OA. It is possible that the examiners were not aware of that part in the reply because they have not read it. That lack of response from the examiners has necessitated including these alternate claims in the next reply with paying additional fees for the claims, and only then did the examiners responded with a rejection. How much merit the rejection had is another question addressed elsewhere. It is also notable that the refusal of the claim drafting, the refusal of making even a comment on these alternate claims in the reply of 2nd OA was coupled with the refusal for phone interview that could have helped to clarify this and other issues including about the lack of the examiners clinical skills. Thus the applicant has endured more then double burden that were against PTO regulations.

B) Another example for refusal of claim drafting is that the examiners have declared **claims 140-143** rambling implying that they were not understandable, and rejected even to deal with these claims in merit, or to offer claim drafting assistance. **(page 3 of last OA)** The PTO examiners also did not bother attempting to clarify these claims through a phone interview (that was even requested by the applicant). The applicant has lost his attorney representation for his US application and could not ask or obtain any help from any US patent attorney. However, in contrast to the PTO examiners who have find these claims rambling and implying that these were not understandable, a Mexican patent attorney had no problem understanding them and suggesting some modifications that would fit the Mexican (but not the US application), taking some non-essential parts out from these claims. Thus the PTO examiners should have been reasonably expected to understand these claims and

comply with the PTO regulation and honor the requested claim drafting. The examiners have failed to do so!

C) As the PTO examiners' comment at page 41 lines 9-13 reveals they in fact did understand what **claims 140-143** were about involving "cost-benefit analysis". However, the examiners did not read the amendment to the specification that they did accept, in which the written description – contrary to the examiners' statement - is present for the allowance of drafting of said claims. In other words: The examiners also declaired these claims a new matter (and they could only do that if they did understand the claims). It is another issue that the examiners did not reed the already amended specification to find the basis for these claims!

6) The PTO has **refused** request for **proper** interview:

At the time of crafting a reply to the 1st OA, the applicant's former attorney advised him that it would be customary for the PTO to honor the requested interview as that request was worded and included in the reply to the OAs, that is if any of the claims would be objected the applicant would request a meeting. That request had been included in all of the applicant's replies, but **was not honored in any instances**. Instead the examiners have issued an office action rejecting all the claims. When - after the first office action - the applicant called the PTO and requested a phone interview, the junior examiner at the phone conference have stated that he is only a junior examiner and has no rights to withdraw from any claim rejection or to commit himself to anything, thus - without the senior examiner being present - the interview was one sided. When the applicant requested to be allowed to have the proper interview with a decision making person that is the senior examiner being present, the phone contact with both examiners were limited to get a denial for such a request. The senior examiner was limiting the interview to two things: She was repeating over and over that the "junior examiner was a good examiner" and also that "it is the law that decides the office action and they know the law". [That implied that the applicant does not know anything about or sufficient amount about that law]. [It was also left out in analyzing the message, that the examiners merely knowing about the law is not sufficient if the application of that law is not correctly applied – e.g. by not reading or ignoring facts from the applicant's submitted material or by not having sufficient (e.g. clinical) knowledge in the field that the examiners were entrusted with to evaluate]. The examiners also stated that the phone interview (that the applicant had with the junior examiner) is limited to half an hour to an hour maximum, but the fact is that the examiners had so many unconvincing reasoning, false logic in he OA(s), besides showing a lack of knowledge in the field, that it is impossible to cover and correct all these in such a limited time. The same is true for an appeal. (If the PTO would get rid of RCE – as reportedly that had been contemplated – that would make the damage caused by the examiners – like in our case - basically irreparable). While a proper phone interview was denied, it was agreed over the phone with both of the examiners that before they would issue the next office action and if the claims would be rejected, the applicant would be allowed a proper phone interview with both of the examiners. The fact is that this promise has never actualized, the phone interview was not granted, but instead the 2nd OA and all subsequent OAs were issued, denying all the claims. Thus the examiners were neither honoring their prior verbal agreement nor the written request in the consequent replies to the OAs to allow a proper phone interview. It is of special note that many of the objections, claim denials, and the examiners' unconvincing line of reasoning could have been cleared and avoided by granting the proper interview.

7) PTO examiners show that they are not even familiar with of what patents have been issued by the PTO for the exact same authors that the examiners bring against the applicant as prior art (**Tollefson 6,960,577** Combination therapy for treatment of refractory depression vs. **last OA p 48 lines 16- 20** WO99/61027). Thus the examiners are making erroneous statements in false support of their argument (and unconvincing line of reasoning) that is coupled with a consequent claim rejection that is not substantiated.

The same is true in other parts of the OA. The examiners give only a speculation, not reading in full the information presented by the applicant. For example, **the 3,539,573 (clozaril) patent** indicate the date of the patent approval in the US for clozaril (patented Nov. 10, 1970). This is in regards of showing that steps similar to the applicant's invention and most specifically to claim number (140-143) are patentable based on the argument previously presented. The applicant has presented documentation to the fact of when the patent term for clozapine expired, and that clozaril (clozapine) enjoyed a patent protection for **over 37 years**! Thus the PTO examiners' speculation on "submarine patent" (see p 43-44 of last OA) is incorrect! The examiners also state in rejecting applicant's claims that "the late expiration of [the clozapine] patent" (which by the way was later then 1993 as stated by the examiners [p 44 line 8 of last OA **vs. reply to 3rd OA page III/13 p.30-36.**]) "does not prove that the Office has issued a second patent ... in view of a new cost benefit analysis". However the examiners ignore the language used by the applicant in his reply that is very specific. It does not have to be the PTO to grant patent extension, there is or are other governmental bodies who can give patent extension **based on the US patent principles** (like the FDA authorized to do so by the Congress). The applicant was very specific, that just because a company for some business consideration decides to get patent protection through another route then a new patent application, that does not preclude the invention to be patentable if the proper submission is filled in a timely manner. The point made here is that for the clozaril's patent extension US patent principles were used as historical data for said inventive steps supports that fact. My recollection is that the treatment resistant schizophrenia consist about 30% of the patients with schizophrenia, and 1% of the population is affected by this disease, thus this is a very lucrative field for pharmaceutical drug development (also taking into account that the cost of the medications is absorbed by Medicare and the society), thus clozaril is not an orphan drug. The applicant in his reply to the 3rd OA has cited the inventive steps that Sandoz (now Novartis) has reportedly stated as a reason of why these steps were not obvious due to secondary factors, and presented the facts that indeed clozaril has enjoyed the continued patent monopoly. [The applicant heard this (that is the drug company claiming the inventive steps and claiming un-obviousness based on secondary factors) from a Mayo Clinic psychiatrist in around1992 when the re-introduction of clozaril in the US was still new, and was coupled with the drug company's fresh marketing effort. The applicant did recently contact Novartis and talked with their representative asking for confirmation on this topic, but Novartis neither returned the call later nor was making a comment on this topic at the time of the phone call]. So indeed with the presented fact that *(a)* clozaril did enjoy an extended patent protection in the US, *(b)* and that all of the elements for a new stepwise invention were present by historical reports and *(c)* that the above referenced non-obvious secondary factors were claimed by the drug company *(that is factors a to c)* indeed do prove that these steps that are similar to the steps of applicant's claims (most specifically to claims 140-143) were in fact patentable. (We are also referring back for additional details to our prior reply). The examiners' line of reasoning was found not to be convincing, and therefore the claim rejection must be withdrawn.

The point made here was focusing on that the examiners were not knowledgeable of pertinent patents (**Tollefson 6,960,577** Combination therapy for treatment of refractory depression vs. last OA p 48 lines 16- 20 WO99/61027), and of the details of the applicant's reply related to the **clozaril patent (3,539,573)**, and not even read the applicant's reply carefully.

8) The examiners are *(a)* repeatedly **misquoting** the applicant (e.g. **see line-by-line reply to the OA below, and see e.g.** 4th OA p. 38 lines 1-3 - compared to reply to the 3rd OA p. 18-21 III2a-III2f,) ; the examiners are also *(b)* **repeatedly carrying over false and unconvincing reasoning** (even when that was sufficiently answered with supported literature) [e.g. last OA p.47 line 16.; see also line-by-line reply to the 4th OA below]; the examiners are *(c)* merely **making a statement without support** and without explanation and without acknowledging of the facts, support and arguments that the applicant has provided to the very same topic, but instead the examiners declairing that no support was provided. (Thus the examiners are ignoring the applicant's reply). [E.g. last OA p.47 line 113-14. compared to written in bold and huge font for emphasis page 28 lines 9-11 of reply to the 3rd OA.]. The examiners are *(d)* also using techniques **misleading** the reader (the "jury"). One of such misleading technique is known in the field and by the trial court attorneys as the "Lincoln technique", that consists of **making a poor summary of what was said** by the other party, leaving out important details and emphasis, downplaying or ignoring said facts, and making an opinion on that poor recap of their own that it is now with all the distortion is not convincing. [see e.g. last OA p.47 line 4-20; see also line-by-line reply to the 4th OA below]. The examiners are *(e)* also **ignoring important facts and details** from the application and replies (in part as stated above under #1-#4). Then the examiners are making their conclusions **unfairly** based upon these poorly crafted office actions rejecting the claims. While the PTO examiners have been empowered with their judicial power to accept or reject an invention, the applicant feels that *(f)* he has received an **unfair trial**, based upon the facts presented herein on how poorly the examiners have handled the office actions. In fact complaint about this in the previous reply (e.g. reply to the 2nd OA page 67-68, big fonts for emphasis) was also ignored and not commented on in the next OA. As said before if the examiners are conditioning their reasoning but these exact conditions they set are unconvincing and the supposedly supporting part of their sentence is false, then the end result and the conclusions including the basis of rejections are also false. (reply to the 2nd OA page 67-68, big fonts for emphasis). The examiners have ignored this feedback on their observed pattern in the next OA. In fact what is odd, that the **examiners are *(g)* using a series of pseudo-scientific methods** (known in the field of psychology and psychiatry – the exact field that the examiners claim having an expertise), and are using such unacceptable methods for creating an impression as if their arguments were evidently supported, as if the invention would be a "prima facie case of obviousness". In fact when reviewed by the applicant (and compared this with some psychology lectures and articles on pseudo-science it was surprising that said pseudo-scientific techniques used by the examiners has **strongly mimicked the profile and techniques used by conmen and psychopaths who want to take advantage of others**. Due to the severity of this resemblance and statement made by the applicant – **under declaration** and to the best of his professional knowledge - the applicant felt compelled to support that with facts, and details on the topic (see below):

<u>On the PTO examiners using pseudo scientific methods:</u>

Pseudo-scientific techniques used by the examiners has **strongly mimicked the profile and techniques used by conmen and psychopaths who want to take advantage of others.**

> Because of the strong nature of the above statement, the applicant feels compelled to make improvement to the society so that other applicants/inventors would not need to endure the same or similar adverse treatment. Therefore he presents the review of these pseudo-scientific and conman methods, and how that resembled the examiners maneuver. Any continuation of these patterns either by the PTO or later by other entities e.g. by not reading the documentations and thus putting extra burden on this applicant would be regarded as continued and planned victimization of the applicant.

8g/A) Confirmation bias.

This is when the positives supporting a point of view are presented ignoring the negatives. (E.g. referencing one study with methodological error but ignoring the wealth of studies, and "making the sale" based on this false "support". "[Not mentioning that it worked in 3 out of 100 patients] but saying it worked for some, therefore it may work for you".

Examples to this by the action of the PTO examiners:

The PTO examiners repeatedly have ignored arguments made by the applicant, have ignored the facts presented (e.g. ignoring the citing the PTO regulations of why the rejection needs to be withdrawn, **(see e.g. as noted under #3 above)** ignoring the presented facts (theory, guidance provided by the applicant, but the examiners repeating to the contrary and repeating the lack of such theory, or evidence. **[see e.g. as noted under #1 above]**).

Other example is that: facts were presented on the unconvincing reasoning of the examiners - like on the antidepressants are acting in the same time frame as the combination treatment - yet the examiners are ignoring this and are repeating their false reasoning "for less time for a therapeutic effect leads to obviousness" (p. 47 line 16 of the last OA **vs. reply to the 1st OA p 59, #22**). Another example is (p 29 lines 12- p 30 lines 2 of the last OA) where the examines argue of what constitutes enablement by the PTO (*not even giving a reference to that rule*), but the examiners in that process ignore important facts: They state that "In order to be regarded as enabled a reference (for example Chappell et al.) must merely describe a process that one skilled in the art could carry out with a reasonable expectation of success". The examiners merely assume "a reasonable expectation of success" and totally disregard the previously presented fact that there is a barrier to overcome that was not enabled in prior art. That is the skilled in the art – against the strong teaching against and against divergent clinical guidelines could not carry out that method – without guidance, explanation and enablement, if it meant that they were risking malpractice! (The examiners still do not understand the clinical thinking and how new information presented by the applicant can overcome such a barrier removing the malpractice obstacle). The skilled in the art without enablement for the purpose of our claims could not be expected to succeed. Therefore alleged "enablement" by prior art can only be stated "existent" on false grounds by ignoring facts that carrying out that process required removal of obstacles (requiring additional steps). Consider a similar example, an inventor submitting an application for a new nuclear plant not with the usual process but with subduing fusion energy, (and let's disregard the fact for a moment if this topic is or is not patentable). The false logic, the unconvincing reasoning by the examiners carried to this example would make this novel and unobvious invention "prima facie obvious" – according to the logic used by the examiners - as this too had been suggested before as a potential option, but no one could do that because the nuclear plant would explode! If you cannot do what the prior art describes because there is an obstacle to overcome for which no guidance was provided in the prior art than in no way can be said of said prior art to be enabling! This is **a logical error by the PTO** examiners not correctly applying the PTO rules. If the prior art is not enabled, the rejection must be withdrawn as we have referenced before the PTO regulations to that effect. (E.g. reply to the 2nd OA page 17-18 last eight and first four lines). The PTO simply ignored these parts in our reply. Yet another example in the same place of the OA is that the examiners are making a statement such as: "The fact, for all practical purposes, FDA regulations and malpractice lawsuits would make it impossible to carry out the method in actual

clinical practice today does not remove the reference as prior art". Now again this is pseudo-scientific while the statement grammatically is correct and portrays a logic and an argument that is word by word true, it is ignoring important and the most relevant fact that we have cited about a prior art: (pasted from reply to the 2nd OA page 17-18 last eight and first four lines):

> "The PTO has disregarded this and the referenced law that **"the examiner cannot use references as prior art if such references have insufficient disclosures." In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..." (page 60 lines 35-42).** The PTO also disregarded the strong supporting secondary factors (pages 93-99) and additional paragraphs of the referenced law (page 98 lines 15-40). Namely, and in putting all of our arguments together (see also page 98 lines 23-31) **the examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references" if the PTO assumes in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219)."

Ignoring the facts, the "negatives" not supporting the examiners false and unconvincing reasoning, and misquoting the regulations and law is misleading, pseudo-scientific, and is **strongly mimicked the profile and techniques used by conmen and psychopaths who want to take advantage of others.**

8g/B) Use of scientifically sounding language.

Use of scientifically sounding language is used by conmen (and pseudo-science) to confuse people. It does not mean it has a basis, but by using scientifically sounding language people does not look it as critically as they could (thus enhancing the false persuasion power). Misquoting the law is an example to this.

> Examples to this by the action of the PTO examiners:
> The PTO examiners have repeatedly used language such as "prime facie case of obviousness" (e.g. p. 47 line 17-18 of the last OA), when the secondary factors, and the presented but ignored evidence was against such a statement.
> At page 50 lines 10-18 the examiners are quoting or misquoting MPEP 2123 and in re Gurley (Fed Cir. 1994). The deciding factor for patentability is not that a known composition is somewhat inferior, but that based on the strong teaching against and based on the available clinical guidelines suggesting a divergent path, the clinicians could not possibly used the method of this applicant without sufficient enablement and without committing a malpractice. (See reply to the 3rd OA p. 43, 44, IV/2).
> (Now it is of note that the examiners are continuing of not understanding the rules for clinical decision making and are perplexing of how come what was suggested but not enabled in prior art can be a malpractice, and how come it is not a malpractice now with proper guidance, new information, with new steps taken by the applicant? The examiners assume that the suggestion in prior art and the applicant's suggestion and invention is "the same act" – which is in fact not the same act as now it is enabled with sufficient reasoning and guidance. - In order to traverse the examiner's objection the applicant needed to show that the examiner had a non-convincing

argument, and the applicant had shown that. However this is a separate issue.) Here we are only focusing of giving examples for the use of pseudo-scientific methods. Another example for misquoting PTO rules (on enablement) was provided under #8g/A).
Another example is quoting and applying only half of the law (and therefore misapplying the law) as we have discussed this in reply to the 3rd OA p. 44 IV/3. Further example for citing and applying only half of the law is in reply to the 3rd OA p.22 III/5. What makes this even more serious is that the PTO examiners totally ignore our reply in this regards and are just pasting the same half part of the law into the 4th OA (p. 14-15) thus misapplying the law. Because of this misquoting the law this pattern is also an example for the next section 8g/C.
Yet another example for quoting and misapplying the law is from p. 31 of the 4th OA, replied herein under line by line reply #XX below in view of alleged inherency discussed under #VIII also under the line by line reply.

8g/C) Appeal to authority, or law of power.
This is another pseudo-scientific techniques often used by conman and psychopaths who want to take advantage of others. [In the non-religious context of using pseudo-scientific technique on people in the US who did not have religious believe of reincarnation] an example for this appeal to authority is of bringing up for support for the existence of "past life/reincarnation" by quoting an "expert" from a well recognized university, in this case from Harvard who was giving an new personal experience for the subjects having hypnotically induced hallucination and under hypnosis an age regression to the imagined past life experience. What is hurtful in this case is misleading the clients to take the experience for reality. Another example for this pseudo-scientific technique is quoting "unnamed experts have find...".
Presenting oneself as an authority is a related technique that can be used and at times is used in a pseudo-scientific way not for the interest of the other person.
Example is referencing the authority or the law in general without specifics, or as for defending for an argument saying "this is a good psychologist, you believe in good psychologists don't you? In fact that does not mean that the psychologist has a good competence for what he or she is pushing for.

Examples to this by the action of the PTO examiners:
With the senior examiner on the phone and denying the proper phone interview, the PTO examiners have made reference that the examiners are the experts, and "it is the law" that decides on the merit of the application, and that they know that law, without quoting any of the law, (intimidating the applicant and implying that the applicant has no knowledge of this law as he is not an authority in the law). The senior examiner instead of engaging into reasoning kept also repeating about the junior examiner "that he is a good examiner, he is a good examiner!"

8g/D) Reliance on the "law of friends" used for self interest and not for the sake of the other. This is too is a technique used by conman in convincing the other person. The person is presenting self as if they were a friend and be interested in the other person's goal, when in fact they are only interested in self serving interest (and often through meta-communication they are revealing that).

Examples to this by the action of the PTO examiners:
At the phone interview the examiner came up with how a rejection could be overcome, just to mention in the next sentence that his suggested way would not work. (see page 6 lines 14-17 of reply to the 2nd office action in reference to the phone interview).

Another example is that the examiner in one prior OA specifically has suggested using a language of antidepressant SSRI, just to reject his own suggestion in his consequent OA – without acknowledging of him making a mistake but implying with his rejecting the corrected claims that the corrections made by the applicant are not acceptable. (In addition, this was improper rejection since the wording of antidepressants, antipsychotics and SSRIs were accepted in numerous other issued US patents are discussed elsewhere under #11).

8g/E) Law of expectancy serving not the other person but self interest.
The person using this method for pseudo-scientific or conman purpose wants the client to buy into his will that does not serve the client but the self interest of the person pushing for it.

Examples to this by the action of the PTO examiners:

At the phone interview with the junior examiner, the examiner has asked the applicant (after his reasoning): "Are you going to abandon your application?" That question implies an expectancy that may make the examiner's job easy, to close the case, but is premature when the applicant's questions and arguments have not been answered yet, or have been repeatedly ignored.

8g/F1) Overwhelming people with evidence of useless information before they have a chance to process them through. Related pseudo-scientific method is the next one:
8g/F2) Throwing these "evidence" or unconvincing arguments so fast and in so many counts that people give up on analyzing and responding. Instead of processing and analyzing the false arguments, it is easier psychologically for people just accepting the presented false and psychologically overwhelming arguments as something true. Example for this is how the tobacco industry overwhelmed the public with false inconclusive studies that they sponsored, and later by a whistle blower CEO with track load of documents. For an ordinary entity it would be impossible to pay for attorneys going over these truckload of documents.

Examples to this by the action of the PTO examiners:

While the applicant's counter-arguments were ignored, the PTO examiners repeated the same data over and over. The total number of pages of the **OA**s is voluminous. It seemed that the same data had been **pasted over again** in many instances, presenting in some aspect a disorganized document to which it is difficult to reply. In order to avoid mirroring the repetition the applicant has tried to overcome this difficulty by summarizing parts that were repeated again and again in the OA and only referencing them in the line by line reply.

Indeed the page numbers needed to reply to the examiners' various unconvincing reasoning and extensive voluminous office actions – with this reply **was** 339+219= **558 pages**. This is in addition to the extensive office actions, the provisional application, the utility and the preliminary amendment. When the applicant has lost his attorney representation (Arni Silverman) he tried to contact his earlier attorney who was filing the utility (Deb Anderson) and who moved to another firm. That attorney has refused to continue to be the applicant's attorney due -in part – due to the extensive number of pages in the office action. It became almost impossible for the applicant to get a fair "trial" and evaluation due to the voluminous nature of the communications from the PTO examiners that is the direct consequence of the great number of their unconvincing reasoning, their unfair techniques used (which we analyze herein), and of the examiners ignoring the applicant arguments which needed to be revisited again in the next reply. It is also notable that reportedly the phone interview is limited to under an hour, and the appeal to 20 minutes. It is impossible to debate the

rejections and the unconvincing reasoning of the examiners in that time frame, when almost every sentence by the examiners can create a mini dissertation on the misleading patterns that they have used. That was also exemplified above, and in the line by line replies. (Specifically see the line-by-line reply to the 4th OA below).

8g/F3) Creating **false sense of credibility with repeated exposure** of the **same unconvincing** illogical **message** (like in the tobacco advertisement the deadly product being attractive) **is a powerful deceptive technique** taking advantage of others. It is different yet related to #8g/F1, and #8g/F2.

Examples to this by the action of the PTO examiners:
The PTO examiners were repeating their unconvincing line of reasoning in numerous counts (as the above examples testify to this effect).

8g/G) Over reliance of anecdotal evidence, over reliance on use of testimonials as evidence, is another pseudo-scientific technique.

Examples to this by the action of the PTO examiners:
This shows an overlap with #8g/B) above, the misquoting the paragraphs of the law or the PTO rulings.

H) Compliance techniques.
This can be used to both to the client interest (like in psychotherapy) and as a coning method to sell something, an idea, of taking advantage of a client.
It should be also noted that **unconvincing and off reality arguments** also has certain logic, like in case of a psychotic person. It is called a **pseudo-logic**. Science fiction movies operate on the same principle it is convincing and grasp the audience on a large scale with the exception that one of the underlying argument is false, and therefore the whole conclusion is false and misleading (even if it is entertaining). In case of the psychotic person or in case of "folie à deux" (**shared psychotic disorder** [see DSM]) the pseudo-logic is also convincing to the person listening. The fact remains that this type of logic is off reality based, and if analyzed correctly they are not convincing for reasoning and should not to be used in trials or by the PTO!
The "yes set" is an example for the compliance technique, when you present trivial things that sounds convincing, and therefore the next part of the argument sounds convincing when in fact it is not if you analyze it. It shows an overlap with #8g/F1) and #8g/F2) above.

Examples to this by the action of the PTO examiners (taken from #8g/F1 and 8g/F2 above):
"The fact, for all practical purposes, FDA regulations and malpractice lawsuits would make it impossible to carry out the method in actual clinical practice today does not remove the reference as prior art". Now again this is pseudo-scientific while the statement grammatically is correct and portrays a logic and an argument that is word by word is true, it is ignoring important and the most relevant fact that we have cited about a prior art: (pasted from reply to the 2nd OA page 17-18 last eight and first four lines):

> "The PTO has disregarded this and the referenced law that **"the examiner cannot use references as prior art if such references have insufficient disclosures." In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..." (page 60 lines 35-42).** The PTO also disregarded the strong supporting secondary factors (pages 93-99) and additional paragraphs of the referenced law (page 98 lines 15-40). Namely, and in putting all of our arguments together (see also page 98 lines 23-31) **the**

examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references" if the PTO assumes in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219)."

8g/I) Distractor; using techniques from social psychology: **The use of "because" creates an illusion that the reasoning had a substance.**
This is related to the above pseudo-scientific technique.
Using a disractor along with a "because" followed by a "placebo information" creates the illusion that the reasoning was explained, but the fact remains that a "because" only creates the semantic for a reasoning and is not a guarantee for the argument. Psychologically it is proven that people tend to accept them for a fact.

Examples to this by the action of the PTO examiners:
4th OA p. 13 lines 11-12: "anxiety is reasonable considered to be a cognitive distortion as it ..." disregarding reply to the 3rd OA p.18 III/2a, - III/2f, and in particular III/2c, and our replies to prior OAs.
Another example is 4th OA lines (9)-10-(13) and lines (13)-14-(16), "One of the ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell..." One of the ordinary skill in the art would have expected success because ..." Compare this with what was said in reply to the 4th OA section VII below.
Further example for the use of this technique is when the examiners with the semantic used are only creating an illusion as if they answered the applicant's argument when in fact they did not. (see 4th OA p. 22 and #XIII of our line by line reply below).

Please also see the line-by-line reply to the 4th OA for other examples, specifically XII around p. 80.

8g/J) A related pseudo-scientific technique to this is the **number of arguments** presented creating a **cognitive load** throwing a whole bunch of information at people **so that they would not process the arguments very critically**. This is related to the examples of #8g/F1, 8g/F2 and 8g/F3, above.

Examples to this by the action of the PTO examiners:
See #XIV p.83 & 84; and #XV p. 87-88; and #XVIII p. 92-93 below.

8g/K) "**Shooting from the hip**" and throwing a bunch of unconvincing line of argument to the other person **putting the burden of proof again and again to the applicant**. This is a pseudo-scientific technique.

Examples to this by the action of the PTO examiners:
As per Arni Silverman my former patent attorney, to my best of recollection he said that at the initial office action the examiners often are using this technique to assess the applicant.
In fact as we have shown in our replies the examiners did this not only in the first OA but in all consequent OAs. The examiners were ignoring facts, presented

unconvincing lines of reasoning (repeatedly, and even after proper attention was drawn to the unconvincing nature of their reasoning). The examiners were putting the burden on the applicant to prove the unconvincing nature of the examiners reasoning, but in the consequent OAs they ignored these proofs and just kept repeating their unconvincing lines of reasoning. The examiners could only get away with this - without acknowledging that they were contradicting to themselves – that they were ignoring the presented facts both from the applicant's replies and from the application; that they were ignoring the secondary factors; and the cited PTO regulations of why the rejection must be withdrawn. This act is not acceptable, it not giving a fair trial to the applicant especially with the vast number of such unconvincing reasoning being coupled with the other tactics discussed herein. (See also the examples from the last OA on clozaril [p 44 lines 11-13] when the examiners were ignoring the context and facts the applicant has presented).

8g/L) Not accepting and dismissing or **ignoring counterarguments**. In order to sound convincing the conman (or the person relying on this technique) is **repeating the same unconvincing line of reasoning** or getting new unconvincing reasons rather then replying to the argument and acknowledging the presented facts. This is pseudoscientific, and in our replies we have shown that the examiners had relied on this "technique".

Ignoring the facts. This is related or often used together with 8g/K) and is also related to 8g/A) above.

Examples to this by the action of the PTO examiners:
Example is ignoring the cited PTO rules of why the rejection needs to be withdrawn, or ignoring the secondary factors (even the existence of them, not even acknowledging that the applicant have mentioned them or that these should be relied upon in making a ruling on the acceptance of the claims.)
Additional examples were listed under #1).

8g/M) Ad hominem attack. Attacking the personality of the other person. This is dangerous for the relationship as it shown in marriage and relationship writings (including my own manuscript). As the explanation of my former patent attorney (in the past), he said that PTO regulation require a gentlemanly communication. I can understand that as attack elicit defensiveness (and in the field of therapy non-compliance). Yet – again talking of the therapy field – limit setting is the number one therapeutic factor in personality disorders (lay term psychopaths). [for reference see Gabard video cited in the application]. I had find it difficult of not to take personally the comments by the examiners, that were overwhelming by their numbers and due to the type of techniques used and discussed herein. I felt that my value system and my sense of reality check was attacked, when I had put up an extraordinary effort and time to make a positive difference in our society, blazing through new trails rather then walking on old paths, to shift our field to a different direction. I perceived that without the financial incentives (of obtaining a patent) the big players needing for the change would not be involved. So when my arguments and the facts were ignored by the examiners, and the examiners have presented unconvincing lines of reasoning and clinically unsounded arguments in such a high number, and declared a "prima facie obviousness" against the secondary factors and against my clinical judgment, there were episodes when I started doubting myself without being convinced. That means that the effects of these pseudo-scientific techniques were working on me. In fact in analyzing of what has happened I could not helped wondering that the very same effects were working on me and against my health that I described under the neuroplasticity changes occurring in every person to adverse environmental stimuli. (That is I wondered that in many ways the techniques analyzed herein had the same effect as the "as if experiment" and the Stanford prison

experiment. Please note that in order to effectively overcome the vast amount of unconvincing reasoning used by the examiners, the applicant had to spend extended time dealing with this issue. This time was more then the two weeks that is the requirement in DSM for the adverse events resulting in depression. In fact the applicant needed to get in all instances (four times) an extension of time (for a total of 6 months each) to complete his replies.
So when I wrote – as a guidance to everyone – that hopefully no one would repeat these adverse experiments causing depression, the techniques used by the examiners had the same direction in their effect then the detrimental "as if experiments" and the Stanford prison experiment I was warning against.

(The extention of time was not created to give time to compensate for the examiners' irresponsive and as it looks like negligent acts. In fact the applicant asks for reimbursement of the fees paid because that time was used for to compensate for the examiners deficiencies).

It was difficult not to perceive these adverse techniques as an attack against myself against my core personality. (The examiners were attacking in an implied way my best judgment and my value system of trusting in the existence of a fair evaluation and trial, didn't they?) Due to the psychologically overwhelming "tactics" I felt I was exposed to I felt discouraged, and I strongly feel that these tactics are not permissible, are objectable on procedural matters, and are unfair. This is why I petition the PTO commissioner herein.

8g/N) **Not committing oneself** to accepting an argument. Evasion.
This is a pseudo-scientific method. You **cannot win an argument this way if the other person is not willing to comment on the argument.**

Examples to this by the action of the PTO examiners:
At the phone contact with the junior examiner he repeatedly said "that he cannot withdraw any rejection or to commit himself to anything as he is only a junior examiner". In the office action he ignored a number of facts, cited PTO rulings, and arguments. (See previously presented examples. Please see examples under #9 below, wherein the examiners first declared that certain new uses were not enabled, then in subsequent OAs the examiners flip-flopped their opinion trying to win on both ends and said that all these new uses were inherent despite the secondary factors we presented to the contrary.
Please also see the example presented under #8g/D on the suggested terminology to be used (like SSRIs) just so that the examiner would flip-flop his own opinion in the subsequent OA when the applicant did his best – enduring time and expenses - to comply with what the examiner has suggested.)

8g/O) Demeaning the other and being abusive, or ridiculing the other with misquoted reasoning. Example to this pseudo-scientific or conman technique is a question: "you don't mean you would succeed with this" forcing the other to give up trying or give up a certain expectation to the detriment of the other person.

Examples to this by the action of the PTO examiners:
I cannot say that the examiners were abusive to me per se, unless all the above tactics would be considered as such. I can tell that in clinical practice and also as my hospital's policy is contesting to that, ignoring a patient is considered a patient abuse. My arguments, stated facts, the described secondary factors, the theory or my enablement were repeatedly ignored. It is up to the reader to decide if these examples consist to abuse the same level as in patient care, when an authority of the

government, the PTO examiners are following such an action. (See also 8g/E as it is related to here).

9) Ignoring by **generalizing, (refusing one argument [or claim], thus refusing all without separate evaluation for the merit** of the others).

Examples to this by the action of the PTO examiners:
When the examiners declared that all the other new uses claimed (like "prevention" for relapse) are "inherent", also implying that they included with said alleged inherency the invention with use of combination treatment being a solution against the paradoxical effect of the antidepressant causing depression and causing suicide. In discussing the secondary factors and citing the FDA directors' inability to give a solution to this problem the small article cut outs were also pasted into our reply. It was impossible for the PTO examiners of not noticing that, unless they skipped through several pages (or were taking the interest of big pharma), yet the examiners ignored this important part also reflected in the claims. No explanation was given in any of the OAs for any logic of how this (that is the antipsychotics effect of reversing or preventing against the paradoxical effect of antidepressants) could be inherent. Please note that the examiners neither brought up obviousness for that effect, nor did they specifically explain any opinion on that part of the statement. The examiners just rejected a group of claims – generalizing – not even focusing on that important part of the invention. This bears with even more importance since the inability of others to provide a solution to this long felt unsolved need was heavily publicized in front page national newspapers and in all prime time media, and that was drawn to the examiners attention in the replies. Please also note that according to PTO regulation the examiners owe a duty for assisting with claim drafting if they see that something could be patentable. Explain it to me please that if the antidepressant has a paradoxical effect of causing depression, then how would it be inherent and obvious that the combination or antipsychotic would be protective of this? We had given guidance in this regard for enablement, but the examiners did not address this question they just rejected the claims. They used the "ignoring by generalizing" technique.
Another example for the examiners "ignoring by generalizing" action are the rejected claims with the wording of "for the benefit of the group" and "for substantially all of said patients".

10) Using contradicting logic, trying to win on both ends.

Examples to this by the action of the PTO examiners:
The examiners first argued that many of our claims were not enabled, then in the last OA shifted their logic and simply claiming the opposite that all these claims were "inherent". The examiners were not taking responsibility for their own action and for what they stated earlier, for their false reasoning, and they were just shifting their statement to say something to the opposite end. (See the danger of this behavior and compare to the content of "Total transformation" CD program).
Please also see the examples provided under #8g/N) and #9) above.
Another example for trying to win on both ends and using a logical error is when the examiners were quoting the Greenich factors as how the patent is granted, but not taking into considerations the very same factors to be used **in allowing the patent for the applicant for his enablement of the long felt unsolved need and for him drawing the right conclusions...** (see also line-by-line reply to 4th OA below)

11) Discrimination.
The question of discrimination is razed based on country of origin and/or of this inventor being a small entity inventor (in particular when compared with how the PTO evaluates and issues patent for big entity inventors like for the big pharma or the Mayo Clinic [heated surgical table example and acceptance ofsecondary factors were in the prior reply to OA]). The applicant feels that he endured hardship due to a discriminative handling of his application compared to others. Examples are presented below. [#11Aa-11Ak and 11Ba-Bb)].

Discrimination may also be present on the basis of disability and of how the PTO rules are crafted. (For example that no extension of time is allowed beyond six months, yet there may be instances when an inventor has an accident, brakes his/her leg, becomes the parent of multiples, or all of the above, making it a hardship to reply within this allowed time frame. In addition additional factors that needs to be taken into consideration that (a) within about seven years time frame that lapsed between the priority date and the evaluation of the patent application (that in this case is still ongoing) a lot can happen in the applicant's ability to properly reply to the OAs. Like in this case (b) it was not the applicant's fault to delay the evaluation process, in fact as we presented the delay was in part due to (c) the unfair tactics used by the examiners and (d) due to other factors on the side of the PTO. This may not affect big entities that much as a small entity inventor who has to do everything by him or herself. The examples for said disabilities therefore may adversely affect a small entity inventor and specifically to the extreme in needing to endure an adverse treatment by the examiners like the ones described.

11A) Discrimination in handling of major drug companies and small entity Eastern European descent inventor who is not represented by a patent attorney, regarding allowance or rejection of words like antidepressants, antipsychotics, or specific groups thereof:

One of the major issue for rejection of the claims and the rejection of the original claims 1-3 was that the examiners assigned to the applicant had a different view on how much the definition of antidepressants and antipsychotics are characteristic enough for the skilled in the art to use our method or if they are infinite. The examiners had claimed that these would depict any antipsychotics and any antidepressants, and rejected the claims. In explaining the examiners argued that in the future many more antidepressants and antipsychotics would be discovered. Applicant argued that in this case no patent could be approved since the use of the words may be extended on any areas to novel not yet conceived product fitting to a major category of a word (e.g. vehicle, table, chair). The examiners argued that the level of scrutiny is higher for pharmacological products and demanded that only a structural description would suffice for acceptance. Please note that the examiners have even rejected when the applicant attempted to overcome said rejection by listing of various compounds from his utility application, or when he have used very specific description again taken from his amended utility application with a feature that can be reproduced describing and fitting any known antidepressants. Please also note that when the applicant had this in the body of the reply asking the examiners to comment on the acceptability of this alternative claim drafting the examiners have ignored that request as non-existent. Request in each reply to call applicant for an interview if claims would be rejected was also consistently denied.

With this background, please note that the US PTO had accepted and issued a vast number of patents for major pharmaceutical companies, where the same scrutiny was not applied:

This also shows that original claims 1-2, or subsequent modification of claims 1-2, and/or their dependent claims were inappropriately denied (as initial treatment – although not emphasized but was depicted by the exclusion criteria).

11Aa) **6,232,326** Nelson, Treatment for schizophrenia and other dopamine system dysfunctions. For dependent claim 14 (dependent from claims 1 and 13) serotonin reuptake inhibitor or norepinephrine reuptake inhibitor were allowed for issued patent as an example.

11Ab) **6,147,072** Bymaster et al. Combination therapy for treatment of psychoses.
In claim 1, atypical antipsychotic and serotonin reuptake inhibitor were allowed in this issued patent.

11Ac) **6,197,764** Bradely et al Clozapine compositions and uses thereof. In claim 20, **anti-psychotic agent** was allowed in this issued patent.

11Ad) **6,599,532** Four et al. Osmotic device containing alprazolam and an antipsychotic agent. In claims 1 and 6, **anti-psychotic agent** was allowed in this issued patent.

11Ae) **6,627,653** Plata-Salaman et al Anticonvulsant derivatives useful for the treatment of depression. In this issued patent a number of various major antidepressant groups were allowed to be used in claim 1, and 6, like mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotoninergic agents, neuropeptides, hormone, atypical antidepressants.

11Af) **6,228,875** Tsai, et al. methods for treating neuropsychiatric disorders. In claim 1, **antipsychotics**, **antidepressants**, and in claim 2, typical antipsychotics, atypical antipsychotics were allowed for the issued patent.

11Ag) **6,727,242** Radulovacki et al Pharmacological treatment for sleep apnea. In claim 11, serotonin receptor antagonist and selective serotonin reuptake inhibitor were allowed in this issued patent.

11Ah) **6,562,858** Oxenkrug, Method for treating depression. In claims 7, 8, and 9, serotonin reuptake inhibitor, tricyclic antidepressant groups were allowed in this issued patent.

11Ai) **6,387,956** Shapira et al Methods of treating obsessive-compulsive spectrum disorders. In claims 10 and 20, serotonin reuptake inhibitor was allowed in this issued patent.

11Aj) **6,831,077** Docherty, Augmentation of atypical antipsychotic agent pharmacotherapy with chromium supplementation. For example in claims 1, and 6 atypical antipsychotic agent was allowed for the issued patent.

As mentioned above the examiners had rejected group of medications for the applicant including the above descriptions that were accepted in numerous other patents, and one of the reasoning of the examiners was that many more such compounds would be still discovered in the future. Please note that the same "logic" that the examiners used against this applicant would then also be true for an overly wide description of disorders, like for "neurological or neuropsychiatric disorder" wherein many more disease are still to be discovered, specifically with the genetic coding of human genomes. To show that the examiners discriminated against the applicant and/or that they used erroneous and non-convincing logic not just for the above group of medications but also in regards

that **prophylaxis**, and **prevention** as used in the medical field does not have to be 100%. (We have argued that in asking for reversing the rejection of our claims on the basis of us using the word prevention). The following issued patent is an example for deviation from the examiners thinking (that is from the examiners assigned to the applicant's invention).

11Ak) **6,310,085** Willis Method for the treatment of neurological or neuropsychiatric disorders. See Claim 1.

Please note that neurological or neuropsychiatric disorders with altered dopamine function is 1) a functional description against which the applicant's examiners reacted with a rejection of claims. Please also note 2) that the "altered dopamine function" would not be much more restrictive (infinite) since it is known that dopamine is responsible for many functions in the brain including being a "reward mechanism", so any neuropsychiatric disorders would have some sort of "altered dopamine function".

The above are just selected examples for one aspect of discrimination and differential negative treatment that is affecting and causing hardship for the applicant.

Other examples describing issued patents had been brought to the examiners' attention in the prior replies. (e.g. Mayo Clinic and heated surgical table and secondary factors; CD disk cleaner).

Yet another examples for the examiners setting a different level of scrunity and higher expectations on this applicant (coupled with the unconvincing line of reasoning from the examiners):
In our reply to the 1st OA (e.g. p.49 and 57 Reply-10 and Reply -20) we have pasted a cut-out from the PDR. The afformentioned antipsychotics not only got FDA approval, but issuance of US patents. No long term or maintenance therapy (and experiments) were required for enablement for those drugs (when the drugs could not be used without long term use), yet the examiners demanded such data for us on "prevention"/inhibiting relapse of depression.

Reply to the 1st OA p. 44, Reply-1: The examiners refused claim allowance of substances identified in professional publications by letters and numbers. Although in lack of time and assistance, the applicant cannot bring up patent numbers, it is his recollection of seing claims identified like that. (Explanation for our argument for why these substances should have been allowed was given at p. 44 of reply to the 1st OA. The PTO ignored our argument and did not comment on that.

Please also note that the applicant doesn't see that the same scrunity and rules were applied for his patent prosecution then for the four issued US patents listed in the applicant's utility p. 5 lines 16-22.

Additional examples for the PTO discriminatory handling of this applicant with the requirement for studies beyond his financial means (a factor discussed previously), maintaining the rejection, when enablement by other means then the requested study was provided:

11B) The PTO accepting "enablement" with "chekmarking" the existence of some studies – when studies are not enabling for all of the claims, only for some of them:

11Ba) Tsai, 6,228,875 above – there is an example on a study on schizophrenia but none on depression, non-treatment-resistant depression and none on initial treatment.
In addition see our reference on gycine as antidepressant already known.
11Bb) Tollefson US6,960,5577 **and the examiners' Robertson argument.**

The PTO examiners err in their reasoning as it is also reflected by the issued patent for Tollefson, US6,960,5577, Combination therapy for the refractory depression. This is also discussed under #VIII in the line by line reply below.

Tollefson US 5,958,921 In this patent the language of "one such study" was used when the studies were said to be on depression – as an inclusive category (see their claims) when in actuality – as the applicant understands it – the study was on Schizophrenia or psychotic disorder (even if the text said, patients not diagnosed with psychosis). Tollefson even published that the drug used in comparison Haloperidol has an depression inducing effect.
Would the PTO accept studies from a drug company wherein in order to prove an "effect" in this case a not yet proven antidepressant effect the study medication (atypical antipsychotic) is compared with a known substance to cause depression (the haloperidol)? This is specifically odd when the inventor himself had (also) published that the substance in the comparison arm does indeed has a depressogenic effect.
(This is the same false logic that would attempt to prove that a sugar pill saves lives when in a double bind expensive study compared to the deadly arsen).
The applicant finds these deceptive and misleading. Please see the details around p 163 (and 166).

To summarize the applicant's point: What is the meaning of a study when it is only used by the PTO to checkmark that a study (and expensive study) was done and thus the claims are approvable even if the study is irrelevant to the claims? Isn't that the PTO was repeatedly doing?
The cited **Genentech 108 F. 3d at 1366** (and other PTO rules) clearly state the requirement for patentability, about the new conclusions to be drawn, and about the enablement requirement. These do not cite any need for expensive and or irrelevant studies.

We have mentioned the $40 Million government sponsored flawed study in our prior reply, wherein one of the antipsychotic olanzapine was used above the FDA approved dose, while the others were underdosed. In research you get the answer depending on how you ask the question and set up the study. The focus should not be on checkmarking the studies but on the merit of the invention with sufficient enablement and with the right conclusions the others could not make.

These additional examples also show that the PTO examiners have handled the applicant's work in a discriminatory way compared to how the PTO treated major entities (several major drug companies or the Mayo Clinic).

These are only some of the major deficiencies and **objections on procedural matters** that we encountered.

The applicant did not want to hurt anybody's feeling, the PTO's, the examiners' of of the "big pharma's"; and even as he feels embarrassed, violated and victimized, he apologizes and feels that he had to write this petition, and that the best course of action was to reveal his findings factually, and write this appeal.

The applicant protest to be exposed to such an adverse treatment that he feels he received (describing the behavior patterns of the examiners). Since past behavior is the best predictor of future behavior, the applicant also protests to be exposed to the same examiners risking further victimization.

Response and amendment to the 4th Office Action (OA) (continued).

Line by line reply – reply to the 4th OA

In this **line by line/section by section** reply to the 4th office action, for better organization, we put our reply in a table. Indented to the left or left column is the copy of the 4th office action's pertinent part, indented to right or right column is or our reply.

(From page 2 of 4th OA)

Claim Objections

Claims 6, 9, 10, 12, 14-35, 37, 41-43, 48, 49, 51-56, 58-94, 96-107, 109-121, and 124-129 are objected to because of the following informalities: the claims contain underlining and strikethroughs to indicate amendments to the claims even though these claims have not been amended in the most recent amendment. This notation creates confusion as to which claims have been amended since the most recent amendment. Rather, underlines and strikethroughs should only be used to indicate the changes made to the claims in the **most recent** amendment. Appropriate correction is required.

#I of reply to the 4th OA:

Compliance is provided herein:

In compliance to page 2 of the 4th OA the following is a correction of the claims of the reply to the 3rd OA - as these claims should have appeared with correct crossed out and underlining. In order to avoid confusion with the current set of claims of the reply to the 4th OA, this correction was put into a box and "– for the reply to the 3rd OA" is inserted after each claim number.
Claim amendments for the 4th OA is shown elsewhere (**p._____**).

Amendments to the claims:

This listing of claims will replace all prior versions, and listings, or claims in the application **as it should have appeared in the reply to the 3rd OA**:

Listing of Claims

1. (Currently Amended – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is ~~a newer antidepressant, and wherein said newer antidepressant is defined as an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase~~ selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

2. (Currently Amended – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as

soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is ~~a newer antidepressant, and wherein said newer antidepressant is defined as an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase~~ selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

3. (Currently Amended – for the reply to the 3rd OA): A method for treatment of a non-psychotic patient having cognitive distortions with functional impairment or health hazards, wherein said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is ~~a newer antidepressant, and wherein said newer antidepressant is defined as an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase~~ selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2

antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, and wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

4. (Original – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is an atypical antipsychotic.

5. (Original – for the reply to the 3rd OA): The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, and pharmaceutically acceptable salts thereof.

6. (Previously presented – for the reply to the 3rd OA): The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

7. (Original – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is a dopamine system stabilizer.

8. (Original – for the reply to the 3rd OA): The method of Claim 7, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

9. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is selected from the group consisting of perphenazine, trifluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride, and wherein said antipsychotic is administered at a low dose.

10. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

11. (Original – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition and an antidepressant with norepinephrine and dopamine reuptake inhibition.

12. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor

antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan.

13. (Original – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein said antidepressant is a selective serotonin reuptake inhibitor.

14. (Previously presented – for the reply to the 3rd OA): The method of Claim 11, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

15. (Previously presented – for the reply to the 3rd OA): The method of Claim 11, wherein said antidepressant is clomipramine.

16. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is risperidone.

17. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is quetiapine.

18. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is olanzapine.

19. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is aripiprazole.

20. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is risperidone.

21. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is quetiapine.

22. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is olanzapine.

23. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is aripiprazole.

24. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is risperidone.

25. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is quetiapine.

26. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is olanzapine.

27. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is aripiprazole.

28. (Previously presented – for the reply to the 3rd OA): The method of Claim10, wherein said antidepressant is fluvoxamine and said antipsychotic is risperidone.

29. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is quetiapine.

30. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is olanzapine.

31. (Previously presented – for the reply to the 3rd OA): The method of Claim 10,

wherein said antidepressant is fluvoxamine and said antipsychotic is aripiprazole.

32. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is ziprasidone.

33. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is ziprasidone.

34. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is ziprasidone.

35. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is ziprasidone.

36. (Currently amended – for the reply to the 3rd OA): The method of Claim 10, wherein said antipsychotic is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

37. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein an effective amount of said antidepressant is its recommended therapeutic dose, or its effective starting dose.

38. (Original – for the reply to the 3rd OA): The method of Claims 1, 2, or 3, wherein the administration is oral.

39. (Cancelled)

40. (Cancelled)

41. (Previously presented – for the reply to the 3rd OA): The method of Claims 1 or 2, wherein said treatment is given for resisting suicide.

42. (Previously presented – for the reply to the 3rd OA): The method of Claim 2, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, -providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said depression.

43. (Previously presented – for the reply to the 3rd OA): The method of Claim 3, wherein said treatment is given at a time selected from the group consisting of, as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for resisting suicide.

44. (Cancelled)

45. (Cancelled)

46. (Cancelled)

47. (Cancelled)

48. (Previously presented – for the reply to the 3rd OA): The method of Claim 1, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, -providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said

depression.

49. (Previously presented – for the reply to the 3rd OA): The method of Claim 3, wherein said treatment is given as an initial treatment, for a patient suffering from major depressive disorder, and for resisting suicide, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

50. (Original – for the reply to the 3rd OA): The method of Claim 3, wherein treatment is given for smoking cessation or nicotine withdrawal.

51. (Previously presented – for the reply to the 3rd OA): The method of Claim 13, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, zimelidine, indalpine, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

52. (Previously presented – for the reply to the 3rd OA): The method of Claim 13, wherein said antidepressant is clomipramine, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

53. (Currently amended ~~Previously presented~~ – for the reply to the 3rd OA): The method of Claim 2, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, inhibiting worsening of said depression from said antidepressant, and treating worsening of said depression from said antidepressant~~,~~.

54. (Previously presented ~~Currently amended~~ – for the reply to the 3rd OA): The method of Claim 49, wherein said treatment is effected for at least one of the group consisting of inhibiting disease progression, modifying the course of said major

depressive disorder, inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said major depressive disorder, avoiding worsening of said major depressive disorder, from said antidepressant, treating worsening of said major depressive disorder from said antidepressant, and treating residual symptoms of said major depressive disorder.

55. (Previously presented – for the reply to the 3rd OA): The method of Claim 1 wherein said treatment is effected for treating substantially all of said patients treated by said physician or other health care provider by said method, wherein said treatment is given for resisting suicide.

56. (Previously presented – for the reply to the 3rd OA): The method of Claim 1 including treating a plurality of said patients by said method, wherein said antipsychotic drug is administered at a low dose, and said treatment is given for resisting suicide.

57. (Previously presented ~~Currently amended~~ – for the reply to the 3rd OA): The method of Claim 2 wherein said treatment is effected for treating substantially all of said patients treated by said physician or other health care provider by said method, and wherein said treatment is given for resisting suicide.

58. (Previously presented – for the reply to the 3rd OA): The method of Claim 2 including treating a plurality of said patients by said method, wherein said antipsychotic drug is administered at a low dose, and said treatment is given for resisting suicide.

59. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

60. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 56,

57, or 58 wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

61. (Previously presented – for the reply to the 3rd OA): The method of Claim 3, wherein said treatment is given for resisting suicide.

62. (Previously presented – for the reply to the 3rd OA): The method of Claim 3, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group.

63. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antipsychotic drug is an atypical antipsychotic.

64. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, and pharmaceutically acceptable salts thereof.

65. (Previously presented – for the reply to the 3rd OA): The method of Claims 1, 2, 55, 57 or 61, wherein said antipsychotic is the active metabolite of risperidone.

66. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

67. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antipsychotic drug is a dopamine system stabilizer.

68. (Previously presented – for the reply to the 3rd OA): The method of 55, 57 or 61, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

69. (Previously presented – for the reply to the 3rd OA): The method of 55, 57 or 61, wherein said antipsychotic drug is selected from the group consisting of perphenazine, trifluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride.

70. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition and an antidepressant with norepinephrine and dopamine reuptake inhibition.

71. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan.

72. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is a selective serotonin reuptake inhibitor.

73. (Previously presented – for the reply to the 3rd OA): The method of 55, 57 or 61, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts

thereof.

74. (Previously presented – for the reply to the 3rd OA): The method of 55, 57 or 61, wherein said antidepressant is clomipramine.

75. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is risperidone.

76. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is quetiapine.

77. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is olanzapine.

78. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is aripiprazole.

79. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is risperidone.

80. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is quetiapine.

81. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is olanzapine.

82. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is aripiprazole.

83. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is risperidone.

84. (Currently amended ~~Previously presented~~ – for the reply to the 3rd OA):~~):~~ The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is quetiapine.

85. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is olanzapine.

86. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is aripiprazole.

87. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is risperidone.

88. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is quetiapine.

89. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is olanzapine.

90. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is aripiprazole.

91. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is ziprasidone.

92. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is ziprasidone.

93. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is ziprasidone.

94. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is ziprasidone.

95. (Currently amended – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antipsychotic is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

96. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein an effective amount of said antidepressant is its recommended therapeutic dose, or its effective starting dose.

97. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein the administration is oral.

98. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

99. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of

protecting against the development of tolerance toward the antidepressant; and remedying the development of tolerance toward said antidepressant.

100. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

101. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

102. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said treatment is given for providing a neuroprotective effect.

103. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said treatment is given for treating residual symptoms of said depression.

104. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of

fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

105. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is clomipramine.

106. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine.

107. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine, and wherein said antipsychotic are selected from the group consisting of perphenazine, tripfluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride.

108. (Currently amended – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine, and wherein said antipsychotic are selected from the group consisting of risperidone, quetiapine, olanzapine, ziprazidone, and aripriprazole, and the effective amount per day is from 0.5mg to 4 mg for risperidone, from 25mg to 400 mg for quetiapine, from 2.5mg to 10 mg for olanzapine, from 10-40mg for ziprazidone, and 2.5mg to 15mg for aripriprazole.

109. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said

major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

110. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

111. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of protecting against development of tolerance toward said antidepressant; and remedying the development of tolerance toward said antidepressant.

112. (Previously presented – for the reply to the 3rd OA): A method for treatment of a

patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of protecting against development of tolerance toward said antidepressant; and remedying the development of tolerance toward said antidepressant.

113. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant -sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

114. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is

selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

115. (Previously presented – for the reply to the 3rd OA): a method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant -sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression

from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

116. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said antidepressant -sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

117. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination

with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is given for treating residual symptoms of said depression.

118. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is given for treating residual symptoms of depression.

119. (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antipsychotic drug wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, wherein said treatment is effected for resisting suicide, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

120. (Previously presented – for the reply to the 3rd OA): The method of Claim 119, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of antidepressant sensitizing patients to depression; treating a paradoxical effect of antidepressant sensitizing patients to depression; for avoiding worsening of depression from the antidepressant; and treating worsening of depression from the antidepressant.

121. (Previously presented – for the reply to the 3rd OA): The method of Claim 119, wherein said treatment is effected at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider, and wherein said atypical antipsychotic drug or said dopamine system stabilizer is administered at a low dose.

122. (Currently amended – for the reply to the 3rd OA): The method of Claims 119, 120, 121, wherein said atypical antipsychotic or said dopamine system stabilizer is selected from the group consisting of risperidone, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

123. (Currently amended – for the reply to the 3rd OA): The method of Claims 119, 120, 121, wherein said atypical antipsychotic is quetiapene, and the effective amount per day is from 25mg to 400mg.

124. (Previously presented – for the reply to the 3rd OA): The method of Claim 10, wherein said treatment is selected as the first choice of treatment, and said treatment is effected for resisting suicide.

125. (Previously presented – for the reply to the 3rd OA): The method of Claim 49, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

126. (Previously presented – for the reply to the 3rd OA): A method for treatment of a

patient having cognitive distortions with functional impairment or health hazards, wherein said patient is suffering from major depressive disorder, wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic, wherein said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

127 (Previously presented – for the reply to the 3rd OA): A method for treatment of a patient having cognitive distortions with functional impairment or health hazards, wherein said patient is suffering from major depressive disorder, wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic, wherein the method comprising administering to said patient an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer and wherein said treatment is effected for resisting suicide.

128 (Previously presented – for the reply to the 3rd OA): The method of Claim 127, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of antidepressant sensitizing patients to depression; treating a paradoxical effect of antidepressant sensitizing patients to depression; for avoiding worsening of depression from the antidepressant; and treating worsening of depression from the antidepressant.

129. (Previously presented – for the reply to the 3rd OA): The method of Claim 127, wherein said treatment is effected at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider, and wherein said atypical antipsychotic drug or said dopamine system stabilizer is administered at a low dose.

130. (Currently amended – for the reply to the 3rd OA): The method of Claims 126, 127, 128, 130, wherein said atypical antipsychotic or said dopamine system stabilizer is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

131. (New – for the reply to the 3rd OA): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase and wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites, wherein said antidepressant is used in combination with an antipsychotic drug, wherein said

antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

132. (New – for the reply to the 3rd OA): A method for treatment of a patient suffering from unipolar depression, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase and wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites and wherein said antidepressant is used in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

133. (New – for the reply to the 3rd OA): A method for treatment of a non-psychotic patient having cognitive distortions with functional impairment or health hazards, wherein said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase, wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine GLY to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites, wherein said antidepressant is used in combination with an antipsychotic drug, and wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

134. (New – for the reply to the 3rd OA): The method of Claims 131-133, wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

135. (New – for the reply to the 3rd OA): The method of Claims 131-133, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

136. (New – for the reply to the 3rd OA): The method of Claims Claims 131-132, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said depression.

137. (New – for the reply to the 3rd OA): The method of Claims 131-132, wherein said treatment is given for resisting suicide.

138. (New – for the reply to the 3rd OA): The method of Claims 131-132, wherein said treatment is effected for treating substantially all of said patients treated by said physician or said other health care provider by said method, and wherein said treatment is given for resisting suicide.

139. (New – for the reply to the 3rd OA): The method of Claims 131-132, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

140. (New – for the reply to the 3rd OA): The method of Claims 1-2, or 131-132, wherein a physician or other health care provider is involving said patient in the

decision-making of said method by discussing with said patient the *risks/benefits,* side effects of the medications, as said physician or said other health care provider is supposed to discussing with said patient the *risks/benefits,* side effects of the medications, and *available alternatives* anyway, *and* since predicting which patients will commit suicide is an impossible task, wherein *the* said method is selected from the group comprising at least one of the following steps (a) wherein a said physician or said other health care provider is taking into account the risk/benefit for a group not just for an individual for said combination use of said antidepressants and said antipsychotics, (b) wherein a said physician or said other health care provider is drawing examples from consisting of how said healthcare providers were treating appendicitis, how said healthcare providers are following similar procedures when giving thiamin routinely for everybody in the emergency room before giving intravenous glucose therefore preventing Korsakoff's syndrome in alcoholics, and how said healthcare providers are routinely testing for drug screen in the emergency room even when the patient says that he or she is absolutely not taking any illicit drugs, in order to point out that said taking into account the risk/benefit for a group not just for an individual is customary in the medical practice, is a standard procedure and good clinical practice, thus needs to be applied for said method, (c) wherein a said physician or said other health care provider is pointing out that in starting said combination use of said antidepressants and said antipsychotics right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor, (d) and wherein in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer said atypical antipsychotics when in a separate diagnostic category from major depressive disorder, in borderline personality disorder said physicians were not afraid of using the combination of antidepressants with antipsychotic medications and when said major depressive disorder has *two to two and a half times more risk for committed suicide.*

141. (New – for the reply to the 3rd OA): ~~(New claim)~~ The method of Claim 140, wherein a said physician or said other health care provider is discussing with said patient other added benefits from the said combination use of said antidepressants and

said antipsychotics wherein said added benefits of said treatment is effected for at least one of the group consisting of inhibiting disease progression, modifying the course of said major depressive disorder, inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said major depressive disorder, avoiding worsening of said major depressive disorder from said antidepressant, treating worsening of said major depressive disorder from said antidepressant.

142. (New – for the reply to the 3rd OA): The method of Claims1-2, or 131-132, wherein the said method is useful for the purposes selected from the group consisting of (a) resisting nonadherence to the prescribed medication, (b) resisting said patients discontinuing, said prescribed medication.

143. (New – for the reply to the 3rd OA): The method of Claim 140, wherein a said physician or said other health care provider is discussing with said patient other reasons and other rationales for using the combination of said antidepressant and said antipsychotic medications in said major depression, wherein said other reasons and other rationales is effected for at least one of the group consisting of discussion of (a) retrospective analysis of suicide committers with major depression showed that many of them have received inadequate treatment (b) it had been shown that among the depressed patients who committed suicide many of them actually had psychotic depression that went unrecognized so they were not receiving antipsychotic medications, (c) cognitive distortions like jumping into conclusions without the analysis of the facts that is prematurely getting into conclusions are characteristic for depression and that it seems that there is an overlap between the cognitive distortions, the mini psychosis of borderline personality disorder, and the full blown psychosis of psychotics, all of them being out of touch with reality but in different degrees and that atypical antipsychotics may be useful for targeting the cognitive distortions that overlap with psychosis (d) the role of cognitive distortions in hopelessness and suicide as a study confirmed the predictive value of hopelessness in suicide, and that hopelessness is the greatest predictor of suicide risk beyond the first year, however suicide occurs in

only five per cent of terminally ill patients and their greatest risk factor is untreated depression, therefore it is not hopelessness per se, but its perception, that is the cognitive distortion characteristic of depression, that seems to be the most important factor, and since for strong perceptual disturbances, said physicians had been using said antipsychotics the adjunctive use of said antipsychotics with said antidepressants in the treatment of said major depressive disorders is supported.

(From page 2-3 of 4th OA)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the **applicant regards as his invention.**

Claims 140, 141, and 143 are rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims contain long, rambling arguments and run-on sentences that make the scope of the claims extremely difficult to understand. It is unclear what practical limitations if any are intended by the argumentation, and the claims as currently written are so confusing that one skilled in the art would not be able to ascertain the true scope of the claims. If the sole point of the argumentation is to support Applicant's arguments as to the patentability of the claims, **then it should be included in the body** of Applicant's arguments/comments. If these arguments are intended to outline a specific set of rationales that the practitioner should discuss with the patient, they should be presented in a more organized and concise form.

Additionally, it should be noted that motivations and mental processes are not in themselves patentable. What is patentable is the concrete **result** issuing form said motivation or mental process.

#II of reply to the 4th OA:
The examiners have failed to point out that how and why these claims would be indefinite. Please note that what we have said under #5/C (as this related to #1). That is that this is an example that the examiners have not read the applicant's submitted materials in full. The arguments presented in these claims were in the amended specification – thus contrary to the examiners note on page 41 lines 9-13 of the 4th OA – this is not new matter and is not lacking written specification in the specification as filed originally.
In addition, it should be noted that while the examiners state that these claims were extremely difficult to understand and were rambling, the examiners did understand that these claims are about the "cost-benefit analysis" (that is about the risk benefit analysis). That becomes clear from the examiners note on page 41 lines 9-13 of the 4th OA.
Furthermore, - and as discussed under #5B and #5C; while the applicant had lost his attorney representation and could not consult with any US patent attorney – the applicant did communicate with a Mexican patent attorney, who did not had any difficulty of understanding and correcting these claims, (as it would fit for the Mexican and not the US application). It was also discussed separately in the petition- objection under procedural matters part) of this reply. Thus this also points out that the examiners had failed to comply with the applicant's claim drafting request under MPEP 707.07(j).
A best effort was done to provide a correction of these claims as the applicant would see it fit for the US application.
The above claims are not "motivations and mental processes, but concrete steps the practitioner must take; they are business methods leading to the result of saving lives."

The above should be discussed in the context of the examiners note on page 41 lines 9-13 of the 4th OA, and of the examiners note on pages 39, 42, 43, 47.. (see also **#XXXII of reply to the 4th OA).**

(From page of 3-5 of 4th OA)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 11, 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121, 123, 126129, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, cited in PTO-892)

Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1, paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1, paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk. **Although treatment of refractory depression is a preferred embodiment, all depression** including depression not found to be refractory, **is included** within the range of disorders to be treated. The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (**p. 1 paragraph 0005**) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard ***as an initial therapy*** and/or to administer it ***as soon as possible***. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, ***and because it is standard practice in the art to administer a therapy promptly once it is indicated***. One of *ordinary skill in the art would reasonably have expected success* because choosing a particular

therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Note that **'as soon as possible" is an extremely broad limitation** that would include practically any method wherein treatment was not deliberately delayed. Similarly, *discussing the risks and benefits* of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and *routine* in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#III of reply to the 4th OA:

The first underlined part the examiners are ignoring my prior reply (not reading it?) in reference of this statement. In particular things being associated or being the same is two different things as my teaching joke form my medical school curriculum on becoming drunk from the ice (alcohol on the rock) picked up this false concept very clearly. (This was presented earlier).

The examiners further argue that the cited prior art from Howard would be understood for all depression not just for treatment resistant depression, and it would have been obvious for the skilled in the art to administer our method as initial therapy as soon as possible within the limitations of our claims. The examiners clearly do not understand the clinical decision making and the thinking pattern of the clinician, and totally dismiss our extensive arguments in the prior replies, including but not limited to the secondary factors, and that the skilled in the art should have been overcoming a strong teaching against and divergent clinical guidelines.

The examiners also ignore that the cited Howard reference was not enabled for the purpose of our claims, and the examiners also ignore the cited PTO rules that rejection based on a prior art that is not enabled should be withdrawn.

The examiners merely making statements with unconvincing lines of reasoning, therefore the rejection must be withdrawn.

The examiners err with their statement that "and because it is standard practice in the art to administer a therapy promptly **once it is indicated**". The point in that statement is the "once it is indicated", however as we have shown it before, at the time of the invention it was not indicated. The examiners merely are using a semantic of "because" without taking into consideration our replies and the divergent clinical guidelines, the strong teaching against that the skilled in the art would have to overcome and other secondary factors.

The **risk benefit alternative** analysis is routine and expected in the art, but with new information revealed in our invention that exact risk benefit analysis is altered and thus what was taught against the method before becomes the enablement for using our method as initial treatment and is supported by the new information presented in our invention.

Thus the examiners reasoning of our invention would be allegedly obvious was not convincing and such statement is not supported.
(See also #VII of reply to the 4th OA)

The examiner also argues that the "as soon as possible" is an extremely broad limitation, leaving out the fact that other parts of the claims wherein this limitation is introduced give the exact boundary precisely further limiting that time frame. (That is to be used for non-treatment resistant depression). Therefore this is not an extremely broad limitation as used in our claims.

(From page of 5-7 of 4th OA)

Claims 1, 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41, 42, 48, 51-53, 56, 58-60, 109118, 124, 125, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al. '921 (US patent 5958921, cited in PTO-892, different from Tollefson W099/61027 cited previously) in view of the Merck manual of diagnosis and Therapy. (Merck, of record in previous office action)

Tollefson '921 discloses a method **of treating major depression comprising administering an effective amount of olanzapine**. (column 1 lines 30-55) A dose of 2.5- 30 mg per day is recommended. (column 2 lines 23-25) Olanzapine can be formulated as tablets for oral administration. (column 4 lines 5-25)

Tollefson **'921 does <u>not</u> disclose a method further comprising administering an antidepressant**, for example one of the various serotonin reuptake inhibitors recited in the claims.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with olanzapine as

disclosed by Tollefson '921. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Tollefson '921 as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Tollefson '921 and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer olanzapine in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#IV of reply to the 4th OA:
Please see other part of our reply (p.163).
Please see the evidence presented that the US 5,958,921 Tollefson reference is misleading or is phrased in a deceptive manner as far as the suggestion for enablement for their broad claims. As it becomes apparent from our discussion the cited study in the Tollefson '921 reference "the patients not diagnose with a psychotic condition" could not possibly involve enablement for the purposes of our claims. Therefore the examiners conclusions are not convincing and the rejection should be withdrawn.
The same what we have said in the previous section about initial treatment, and about the risk benefit analysis also applies here.

The examiners were also ignoring the secondary factors we have presented in our prior replies.

(From page 7-12 of 4th OA):

The following rejections of record in the previous action are

maintained: ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 95-103, 126, and **131-143** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does **not reasonably provide enablement** for such a method involving **any antidepressant** whatsoever. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More generally, the full limits of the class of compounds known under the various functional groupings (e.g. selective serotonin reuptake

inhibitors, selective norepinephrine reuptake inhibitors, antidepressants with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, antidepressants with serotonin/norepinephrine/dopamine reuptake inhibition, etc.) recited in the language of instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally.. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

The Breadth of the claims: The claimed invention encompasses combination therapies of any of a number of functionally defined groups of antidepressants with an antipsychotic. The antidepressants are defined only by their functional characteristics.

In particular, a vast number of different structures are included within the limits of these claims.

The amount of direction or guidance presented: Two hypothetical cases

are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

The presence or absence of working examples: No working examples of the claimed therapeutic methods are provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of the various functionally defined groups of antidepressants, one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Animal experiments include, along with the actual administration of the potential

pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of synthesis, *in vitro,* and *in vivo* testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, "**a patent is** not a hunting license. It is not a reward for search, but **compensation for its successful conclusion**." And "**patent protection is granted in return for an enabling disclosure of an invention**, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with all of the compounds falling within the recited functional groupings of antidepressants.

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

#V of reply to the 4th OA:

Please see the facts presented under #11A, and in particular #11Aa) - #11Ak) above with the corresponding vast number of issued US patents using the same terms that the examiners are declaring would make our claims not enabled thus rejecting our claims.

Please also note in our arguments in prior replies in this regard. **(In particular attention to discussion on what should concern the patent office according to my previous patent attorney's explanation when he was still representing me. A modification with a new invention is patentable even though the inventor cannot use it without permission of the previous patent owner. Therefore, the examiners "worry" of taking incentives away for new development is unfounded.)**

Please also note that the examiners did contradict their own previous recommendation (e.g. to use the term SSRI). The examiners err on requiring a structural description and rejecting other definition and functional description being insufficient. The vast number of US approved patents listed above is a testimony in this regard.

Furthermore we have presented alternate ways to overcome the objection for any antidepressant in claims 131-139.

The examiners also err in trying to win on both ends of an argument, they bring against us as a prior art of aripriprazole being enabled on the basis of not even having the same as the receptor profile of the compound being compaired to, just having a similar receptor profile than the compounds mentioned in that reference the PTO listed.

In addition the examiners are making false statements and are basing the rejection on these very same false statements as for false support of their unconvincing reasoning: (e.g.: page 9 lines 9-11 of the 4th OA: It seems that the examiners did not read our reply and our application, as our theory, guidance and enablement was specifically spelled out).
The examiners are citing the **Genentech**, 108 F.3d at 1366, that sates that, **"a patent is ...(a) compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention."**
These very reasons actually are supporting that the applicant should be issued the patent, in particular of the number of secondary factors.

Additionally, claims 140-143 were grouped into this rejection when they are clearly enabled on different way in the specification.

(From p. 12 of 4th OA):

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See *in re Smith,* 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

#VI of reply to the 4th OA:
We have discussed this in our prior replies, (active metabolite) Give new reasoning, This is a "vice versa" reasoning of PTO, bringing up that juice may lack other active ingredient. The logical error is: that our description gives the analogy that if grape has the active ingredient then grinding it with your teeth the resulting grape juice also would .– (and you would still swallow the other parts – therefore the inherency is there). Therefore the cited articles enclosed in the last OA in this regard are irrelevant to our argument.
We have said earlier that if the other claims would be accepted, it would not worth fighting for us over this issue.

(From p. 12-15 of 4th OA):

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, 126-130, and 140-143 are rejected under 35

U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a **D4 receptor antagonist**, (an antipsychotic) and a pharmaceutically acceptable carrier, (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph

0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. **as an initial therapy** and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima fade case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ

90 (CCPA 1976); In re *Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Further, discussing the **risks and benefits** of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108, 131-134, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) in view of Berman et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima fade* obvious.

#VII of reply to the 4th OA:

The PTO disregarded our prior argument on D-4 receptors and the lack of enablement in prior art. The PTO examiners are making their rejection basically repeating their unconvincing line of reasoning from the prior OA. To avoid increasing disorganization in the correspondence, we hereby link what the PTO has said here with their later note at page 35 of the 4th OA. However, the PTO examiners have still failed to sufficiently address the applicant's reply to the 3rd OA in particular III/1 and III/9 p.(18-43). Therefore the PTO examiners' statement remains unconvincing. We have cited documentation that the mere D4 activity does not ensure antipsychotic action! Just because some agent showed antipsychotic activity in animal models as the Krammer reference attest to that it does not prove antipsychotic action. Just because Chappell recited the antipsychotic olanzapine as D4 receptor antagonist, this is not an assurance that the antipsychotic action of olanzapine would be due to the D4 activity. In fact it is highly likely that if the D4 receptor would be blocked in an experiment with another agent (not having an agonist or antagonist effect on that receptor) olanzapine would still have its antipsychotic effect (e.g. through the D2 receptor). The PTO disregarded the applicant's more detailed argument from the reply to the 3rd OA (p.18-43). The PTO did not show that what percentage of the olanzapine's action would be due to the D4 activity – if any, and if that a lone would be sufficient for an antipsychotic action compared to placebo!

It is of note that the historical speculation that the atypical feature of an antipsychotic would be linked to the D4 receptor was not proven and that idea was abandoned.

The fact that Chappell abandoned his application and did not provide enablement for his mere suggestions makes the lack of enablement even stronger. The PTO examiners have repeatedly ignored the cited law of (e.g. p 36 of reply to the 3rd OA):

> **In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."**
>
> **"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public**, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

The PTO then declares that "anxiety is reasonable considered **cognitive distortion**" and completely disregards the applicant's prior reply to the 3rd OA (p. 18- 21 III/2a-III2/f), and the arguments given even in preceding replies. The PTO examiners brief note on page 38 of the 4th OA is not addressing this issue: lines 1-3 is a misquote [compare that with reply to the 3rd OA (p. 18- 21 III/2a-III2/f)]. The sentence of line 3-6 of page 38 of the 4th OA is irrelevant to the applicant's arguments. Lines 6-8 is incorrect for a reply and is misleading: Since the PTO has failed to show any prior art in regards of using the invention the antipsychotics and the combination therapy for cognitive distortion, and the PTO has based their

rejection solely based on the PTO examiners' unconvincing line of reasoning, the only thing the applicant had to show that the PTO had an unconvincing line of reasoning. The applicant had shown this. The PTO had also **failed** to show that the antipsychotics would indeed act on the cognitive distortion – an that would be recognized by prior art - and consequently the anxiety (or depression) would be decreased because of that effect. The PTO failed to show that such an effect was recognized by prior art and by the skilled in the art. Therefore the PTO statement (p 38 lines 6-8) for the PTO needing to "merely" show that cognitive distortion is one component of the anxiety is an incorrect statement and an unconvincing line of reasoning. There is no prior art that we are aware of that would show that the aforementioned medications get their desired effect by targeting cognitive distortions. In fact prior art on the effect of medications is focusing on receptor profiles and not other enablement. Therefore the PTO has failed to show any existence of obviousness.

The PTO examiners then argue that it would have been obvious to use Chappell's not enabled method as an **initial therapy** and give false reasons like "because it is a standard practice in the art to administer a therapy promptly once it is indicated". The point is on "once indicated" and it was not indicated! The fact is left out that the secondary factors show that differently as there was a strong teaching against of using the method (as initial therapy), and divergent clinical guidelines were present. It is difficult to argue with the examiners if they don't read and ignore the applicant's reply, and if the PTO ignores the supporting secondary factors.

The "*In re Wertheim*" was discussed earlier [see 8g/B)]. In addition the Chappell reference did not enable our method at any dose!

The discussion with the patient on the **risk benefit alternative** analysis is indeed the responsibility of the healthcare provider, however, the PTO leaves out the important detail that that was done at the time of invention according to the standard of care with the strong teaching against using our method, having a divergent clinical guideline in place – as far as our claims and the initial treatment. The previously attached publications are supporting this as secondary factors. Therefore the PTO's argument is unconvincing that the skilled in the art would have come to the same conclusions as the inventor with the same sufficient enablement for the method. The guidance and overcoming the barriers were not available till the applicant's invention. As for proof the secondary factors, testify to that effect and to the unconvincing nature of the examiners' argument. There was continued teaching against the method, with divergent clinical guidelines. Even years later on the paradoxical effects of the antidepressants causing suicide the FDA directors showed inability in front page media interview to provide a method for a long felt unsolved need solved by the applicant.

Of note, the PTO examiners did ignore the secondary factors along with the applicant's reasoning, and the cited laws of why the rejection must be withdrawn. It is difficult to win an argument with such an unfair evaluation process.

Since rejection under the Chappell reference must be withdrawn, the examiners next statement (over Chappell in view of Berman) looses its importance. Of note,

we would like to mention that prior art would not render our invention obvious for initial treatment for ketamine, for the same reasons that we have discussed above (like the importance of new risk/benefit/alternative analysis, and for the secondary factors).

(From p. 16- 17 of 4th OA):

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A **person** shall be entitled to **a patent** unless —
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 127 and 128 are rejected under 35 U.S.C. 102(b) as being **anticipated by Robertson** et al. (Reference of record in previous action)

Robertson et al. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry

and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The intended uses recited in the instant claims, for **example inhibiting the development of tolerance toward an antidepressant**, providing a neuroprotective effect, **avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation**, and **delaying or resisting relapse**, are ***inherently present*** in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at *elevated risk for suicide*, and could suffer relapse after treatment.

Therefore the claimed invention is anticipated by Robertson et al.

#VIII of reply to the 4th OA:

The PTO examiners err in their reasoning as it is also reflected by the issued patent for **Tollefson, US6,960,5577,** Combination therapy for the refractory depression.

The PTO examiners repeat the same unconvincing line of reasons that they have repeated so many times earlier including previous OAs. The PTO examiners did not understand and/or disregarded the applicant's reply to the 3rd OA (p. 52-55.) Instead of repeating, we refer back to that part.
It is of note that the applicant had disclosed in the provisional and utility application the historical background of the treatment of depression (page 1-2 of the utility):

> "The first treatments for severe mental disturbances became available in the 1930's, when extracts from the plant rauwolfia serpentina were used for the amelioration of psychotic symptoms. Major advances in the treatment of psychosis, however, did not come until 1950 with the discovery of chlorpromazine. The first generation of antidepressants did not become available until the 1950's, and included monoamine oxidase inhibitors and tricyclic antidepressants. While chlorpromazine was used early on in the treatment of depression, as tricyclic antidepressants became available the use of antipsychotic medications declined, and they were never widely used in the treatment of depression in the absence of psychotic symptoms. See also Raskin A. et al 1970, p.170: "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical

antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)"

The applicant had also referenced the Robertson article (page 2 of the utility 5th paragraph). Therefore it is surprising that the examiners did only bring this objection to the applicant's attention with the 3rd OA. Never the less the examiners err in their conclusions:

The examiners at p. 49 of the 4th OA lines 4-8 incorrectly state that the teaching of Robertson falls within the claimed invention. Robertson did not use the same medication combinations of our claims. In fact our claims specifically excludes the older antidepressants.

The examiners also err in concluding that anticipation can occur based on Robertson for a new class of drugs, when with time a consensus developed:

See utility p. 2 last 2 lines and p. 3 lines 1-8:

"A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987). The combination use of these medications to treat non-treatment resistant, and non-psychotic depression was never recommended. A book chapter reviewing this topic from year 2001 makes the point that "the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,)."

With time a strong teaching against and divergent clinical guidelines developed, (in particular as regards of what strategy to use for initial treatment) so by the time the newer and safer antidepressants were introduced anticipation for our claim from Robertson could not possibly exist. Therefore, what the examiners (p 49 of 4th OA) state that "a rejection for anticipation under 35 USC 102(b) is a statutory bar and no secondary considerations can serve to overcome it" word by word may be true but not as it should be applied here. If there is no anticipation then is not the secondary factors that makes our claims patentable, but that there was no anticipation. The secondary factors only show that indeed the anticipation by the killed in the art did not exist. (See also previous attachment/publications on secondary factors). Therefore the examiners are using a logic that is not convincing.

What we have said before on cognitive distortion, anxiety, and our new risk/benefit/alternative analysis would be equally applicable here.

Also the PTO examiners only made a statement without explanation on the alleged inherency. Please explain to me the PTO examiners false logic: If an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression, and/or there is a tolerance developed for the antidepressant, how can our claims be inherent for "inhibiting the development of tolerance toward an antidepressant", "avoiding worsening of the depression [that is caused by the antidepressant itself]"?

Similarly we have shown that depression and suicide is not necessarily correlate, and that you can resolve the suicidality in an instant when the

depression persists. [see what we said about Victor Franckle]. Therefore resisting suicide, avoiding suicidal ideation is not inherent. In addition - as we said above - when an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression and causing suicidal ideation and suicide, then how can our method of administering our treatment in our claim be inherent?
The examiners just grouped things together and used a "reject one reject all" principle (see objection under procedural matters #9 above).
Delaying or resisting relapse - when there is a factor that tolerance may develop toward the antidepressant or that the antidepressant may paradoxically worsen the depression - in no way should be considered "inherent", or the examiners should come up with some type of explanation for how can all these happen.

This reply applies to any other (repeated) rejection from the examiners on the same topic.

(From p 17-18 of 4th OA):

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action) The disclosure of

Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#IX of reply to the 4th OA:
This is related to #VII above.
The PTO examiners have failed to sufficiently address the applicant's reply to the 3rd OA in particular III/1 and III/9 p.(18-43). Therefore the PTO examiners' statement remains unconvincing. We have cited documentation that the mere D4 activity does not ensure antipsychotic action! Just because some agent showed antipsychotic activity in animal models as the Krammer reference attest to that it does not prove antipsychotic action. Just because Chappell (in view of Schmidt) recited the antipsychotic ziprasidone, risperidone, or quetiapine as D4 receptor antagonist, this is not an assurance that the antipsychotic action of ziprasidone, risperidone, or quetiapine would be due to the D4 activity. In fact it is highly likely that if the D4 receptor would be blocked in an experiment with another agent (not having an agonist or antagonist effect on that receptor) ziprasidone, risperidone, or quetiapine would still have its antipsychotic effect (e.g. through the D2 receptor). The PTO did not show that what percentage of the afformentioned antipsychotics' action would be due to the D4 activity – if any, and if that a lone would be sufficient for an antipsychotic action compared to placebo!
The PTO disregarded the applicant's more detailed argument from the reply to the 3rd OA (p.18-43).
It is of note that the historical speculation that the atypical feature of an

antipsychotic would be linked to the D4 receptor was not proven and that idea was abandoned.
The fact that Chappell abandoned his application and did not provide enablement for his mere suggestions makes the lack of enablement even stronger. The PTO examiners have repeatedly ignored the cited law of (e.g. p 36 of reply to the 3rd OA):

> **In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."**
>
> **"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public**, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

In addition it is notable that Chappell did not enable our method!

(From p. 18-19 of 4th OA):

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#X of reply to the 4th OA:
The same what was said under #IX (and #VII) above applies here with the substitution of the names of antipsychotics recited herein in view of Roth.

In addition it is notable that Chappell did not enable our method!

(From p. 19-21 of 4th OA):
Claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, 129, and 141143 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Robertson et al**. (Reference of record in PTO-892) as applied to claims 126-128 above, and further **in view of the Merck** Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference included with PTO-892, herein referred to as Merck) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a therapy comprising a combination of a typical antipsychotic with a newer antidepressant. (i.e. an antidepressant that is not a tricyclic or tetracyclic antidepressant or a MAO inhibitor) Robertson et al. does not explicitly disclose a method of administering the claimed

treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. **as an initial** therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to

administer the antipsychotic in a **low dose**. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the **risks and benefits** of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#XI of reply to the 4th OA:

The same what was said above in particular under #VIII above applies here. The examiners unconvincing line of reasoning was discussed under #III, and VII, in regards to initial treatment, and an old risk benefit alternative analysis allegedly being the same as our new inventive one that was overcoming the obstacles and teaching against our method.

low dose, was discussed in prior replies and is discussed again later.

(From p. 21-22 of 4th OA):

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Robertson** et al. (Reference of record in PTO-892) **in view of Berman** et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

#XII of reply to the 4th OA:
We had sufficiently discussed this in regards to Robertson under #VIII, and the "in view of Berman under #VII.

(From p. 22 of 4th OA):

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection, for reasons recited as regards the rejection over Chappell et al. in view of Berman et al.

#XIII of reply to the 4th OA:
The examiners are only making a statement, without giving an explanation

whatsoever. The "reasons recited" are the same as in their previous OA and therefore the examiners are ignoring the applicant's reply.

The "for the reason" is working here the same way as "because" described under the tactics of pseudo-science (8g/I). With the semantic used the examiners are creating only an illusion as if they did reply to the applicants argument.

(From p. 22 of 4th OA):

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 5164, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, 124-129, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Pivac** et al. (Reference included with PTO-892) **in view of Merck** (Reference included with PTO-892) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an **initial therapy** and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a **low dose**. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Similarly, discussing the **risks and benefits** of a therapeutic method with

a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#XIV of reply to the 4th OA:

The PTO examiners are only repeating as the basis of their rejection what they have said in the previous OA ignoring the applicant's extensive reply with supportive documentation.

The examiners do give later (p 51-52 of the 4th OA) a brief brush off only for selected arguments that is not acceptable and not a convincing reasoning:

First we need to refer back to our reply to the 3rd OA, in particular p. 58-62, for the sake of avoiding repetition.

Second, the PTO is making several logical errors in brushing off our reply.

Notably, that the PTO examiners are totally ignoring and not even considering for a mentioning #IX/1 of our reply that the Pivac reference is not enabling, and according to the cited regulations the examiners cannot use references as prior art if such references have insufficient disclosures.

In addition the examiners make some incorrect statements on p. 51 of the 4th OA. The Ferris reference actually deals with a newer antidepressant buproprion, and as per the examiners' statement the SSRI antidepressant was already known at that time and was even in use. The Ferris reference is very much relevant to show that while antipsychotics augment antidepressants including buproprion, the speculation on receptor profile does not stand scrutiny because of Ferris and also the other cited references. (see p. 58-62 reply to the 3rd OA). So the examiners are incorrectly brushing off the applicant's reply.

Furthermore, in lack of prior art teaching the same then our claims, the examiners presented during the course of their OA numerous unconvincing line of reasons. The applicant job was to point out the unconvincing nature of the examiners reasoning, witch should have resulted in the withdrawal of the rejections. Therefore the examiners are incorrect saying (last paragraph of p 51 of 4th OA) that – when we have shown that the examiner's lines of reasoning was not convincing, the examiners are rephrasing that fact to "uncertainty" as to the reason for the synergistic effect between certain antipsychotics and antidepressants.

The examiners following lines are also incorrect and out of context at p. 52 of 4th OA. The examiners state that "merely showing that the method by which an invention works, as is the case with the Toth, Roth, and Cremers articles, is not fully known does not keep one of ordinary skill in the art from using it." Sorry, but our method in prior art was never used for unipolar, nonpsychitic -non-treatment resistant depression, period! So the examiners statement is misleading as they do assume (1) that prior art enabled our method when it did not, (2) and that the skilled in the art at the time of our invention it was obvious that our method would work and should be used! None of these assumptions are correct! It was only the examiners who came up with unconvincing lines of reasoning making false

assumptions, ignoring the facts we presented, ignoring the massive amount of secondary factors that we have presented in our replies and with our attachments. Therefore our argument was not that *"the method by which an invention works, ... is not fully known"*, but what we have shown was that the speculation that the examiners had presented were not convincing based on several prior art publications. The second part of the sentence is also an incorrect assumption *the method by which an invention works, ...does not keep one of ordinary skill in the art from using it."* The secondary factors showed that the skilled in the art did not use our method for the purpose of our claims. As we said at the beginning of this petition and objections on procedural matters under 8g/F2 it is psychologically overwhelming of analyzing each part of the examiners sentence for a number of incorrectness, and it is easier for the reader to just accept the false statements as if they were convincing and true. This pattern of the examiners is dangerous.

The next sentence by the examiners (still on p 52) is also incorrect, misleading as if that would be a valid reason for their rejection and for disregarding the applicants reply: The examiners say: *"the cited prior art* [i.e. in order to show that the PTO examiners did not have a convincing line of reasoning] *does not show that atypical antipsychotics to not work to augment the effects of antidepressants..."* That is not what the applicant needed to show. In fact if he would show that, that would invalidate his invention. So the examiners semantic sound logical, creating an illusion of being "convincing", but it is not directed to what would be needed in order to a legitimate rejection of the applicant's reply and claims. So looking the second part of this sentence by the examiners we see that it contains again an incorrect statement:

"The cited prior art does not show that atypical antipsychotics to not work to augment the effects of antidepressants ***but*** *merely that they might exert this effect in a different manner than was supposed by Pivac et al.* Actually, the cited prior art by the applicant does <u>not</u> show at all that atypical antipsychotics work to augment the effects of antidepressants in a different way. That is only the examiner's assumption. It was the applicant who enabled his method in a way never described in prior art! This is a huge difference in particular with the new path the applicant was walking with his invention and with his new conclusions he made. Isn't this what Genentech, 108 F.3d at 1366 says for why patents are granted?

The examiners' last brushing off argument does also not stand the scrutiny when analyzed for if it is logical. (That is again the examiners show unconvincing line of reasoning as a basis for rejecting the applicant's reply and claims).

"The one reference showing a clear negative teaching, Perez et al., concerns patients with depression resistant to SSRIs. Because the claimed invention specifically deals with non-treatment-resistant depression this teaching that pindolol does not overcome treatment resistance is <u>not relevant</u> to the claims." (???)

Why is it irrelevant, please explain it to me? The PTO failed to do so.

First (as for this PTO section) the PTO assumes that anticipation or obviousness occurs because Pivac merely states that there is a synergistic effect that Pivac by the way did not enable. Second, we had shown that the speculation to explain such synergistic effect through said receptor mechanism does not work as several prior art papers attest to that. In fact that very same paper by Perez on pindolol also is in support that the said speculation on receptor subtypes would not work. This fact is

regardless of treatment resistance. It is very much on disproving the speculation by Pivac – (see IX/5 p.59 of reply to the 3rd OA). When the PTO was confronted that if there was no enablement and speculation based on said receptor subtypes was shown in prior art of not working, that is that there is nothing then to support anticipation or obviousness; the PTO brushed off this by saying that this *"does not keep one of the ordinary skill in the art of using it" [i.e the method* –see p. 52line 3 of 4th OA]. Now, what kind of logic is that? This makes no sense! The secondary factors also support us that there was no anticipation or obviousness! However, the PTO did disregard the presented secondary factors too!!!
In addition the examiners had dismissed several other arguments like #IX/3 of reply to the 3rd OA. Our invention is different from prior art, including initial treatment, the new risk/benefit/alternative analysis and this too was dismissed with unconvincing line of reasoning that we had discussed earlier.

(From p. 24 of 4th OA):

Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 7074, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Jordan** et al. (PCT international publication W002/060423, reference included with PTO-892) **in view of Merck**. (Reference included with PTO-892) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference included with PTO-892) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 – p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in

combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is

within the routine and ordinary level of skill in the art.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *in re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In *re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima fade* obvious.

#XV of reply to the 4th OA:
The PTO examiners just repeat what they said in the 3rd OA, without taking the applicant reply to consideration.
The only reply is later at page 52 lines 11-14 of the 4th OA. However the examiners' "brush off" makes no sense and does not show any logic at all in relation to the applicant's reply to the 3rd OA pages 60 #IX/5-B and pages 64-68 #X/1-#X/9.

> *"The Jordan et al. reference concerns aripiprazole, which has a different method of action from atypical antipsychotics, being a partial agonist of the dopamine receptors. Therefore results concerning aripiprazole are not directly relevant to the atypical antipsychotics which are different molecules with a different receptor profile."*

We have not made any argument on aripriprazole what the PTO indicates that would not be relevant for the reason they indicate. We did reply to the claim rejection that was ignored by the PTO.

Furthermore the PTO misquotes the Jordan reference as if the examiners language had been used in that reference. Notably, they state that the compound is useful for treating major depression, when that reference was not enabled for the purpose of our claims. (And as discussed in our prior reply.) The Jordan reference did not make mention on using the compound for cognitive distortion. In fact no prior art or no publication up to date is recommending that. Aripriprazole was not even used for treatment-resistant depression at the time of invention. Even up to date the compound was only used in treatment resistant depression.
The PTO also errs with his statement that it would have been obvious for the skilled in the art to use aripriprazole for the purpose of our claims, when it is notable that the average skilled in the art would not even had access to the compound as special permits are needed for investigational non-approved medications. So the PTO examiners make false assumptions when they are not reading and not answering the applicant's reply.
The other unsupported comments on alleged obviousness like initial treatment had been discussed earlier.
On page 53 of the 4th OA the PTO refers back to their the previously discussed unconvincing line of reasoning (under Pivac).
Note that the Jordan reference attempted to "enable" aripriprazole by compairing the receptor profile of that compound to buspirone. (So the Jordan reference looks like - according to Genentech, 108 F.3d at 1366 - a vague imitation, specifically when for "enablement" comparing aripriprazole to compounds that does not even match the receptor profile of aripriprazole). So when the applicant shows (#X/2a-1 and #X/2a-2 of reply to the 3rd OA at page 65) that buspirone in double bind placebo controlled prior art study was not more efficacious then placebo when augmenting an SSRI that is very much relevant information, and this is regardless of the study being on treatment-resistant depression. What we had to show was that the PTO came up with an unconvincing line of reasoning of why the skilled in the art would have found the Jordan reference – based on receptor profile similarities – not obvious. We have proved that. The PTO brushing off the reply by saying that the examiners are not concerned of what the practitioners are not doin. That is the PTO is not concerned of the secondary factors??? (What the PTO is saying with that is that they are not concerned of the practitioners not using the buspirone off-label as augmentation of antidepressants, therefore the PTO is not concerned that the alleged obviousness is declared only by the PTO! Now I'm speechless again by the non-sensual nature of the PTO examiners' presented logic! And this type of reasoning is repeated again and again psychologically overwhelming the listener, giving in that it is easier to accept that false argument then to flip over several documents and see what was really said in the reply or in these prior art documents.

Note that the Jordan reference attempted to "enable" aripriprazole by compairing the receptor profile to another. Please note from the data available form SSRIs' that having the same receptor profile (like fitting into the SSRI category) is not an assurance for an antidepressant effect as the experience shows as many of the SSRIs were dropped from clinical studies for not being more effective then placebo.

(From p. 27 of 4th OA):

Claims 106-108, 131-133, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Jordan** et al. (Reference of record in PTO-892) in view of **Berman** et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima fade* obvious.

#XVI of reply to the 4th OA:
The PTO examiners just repeat what they said in the 3rd OA, without taking the applicant reply into consideration, and ignoring the applicant's reply.

(From p. 28 of 4th OA):

Claims 3-5, 9-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Theobald** et al. (US patent publication 2003/0049308, first published as PCT international publication W001/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating **nicotine dependency**, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal.

Thus the invention taken as a whole is *prima facie* obvious.

#XVII of reply to the 4th OA:
The PTO examiners are repeatedly under the false pretence that just a mentioning something that is against a strong teaching against and against divergent clinical guidelines would be sufficient for enablement. That is far from the truth when additional barriers for the use of the method would need to be overcome with taking additional steps.
The new risk-benefit-alternative analysis and initial treatment is example to that.

The same misconception is applied here by the PTO. (see p. 54 lines 9-10 of the 4th OA)
Otherwise the examiners are repeating what was said in the 3rd OA and are ignoring the applicant's reply (p.70 reply to the 3rd OA)

(From p. 29-30 of 4th OA):

Response to Argument

Applicant's arguments, submitted May 1, 2008, with respect to the various grounds of rejection above, have been fully considered and not found to be persuasive to remove the rejections. Reasons that the arguments were not found to be persuasive are discussed below:

General issues raise by Applicant

Before addressing the specific grounds of rejection under consideration, several issues will be explained in order to clarify the reasons for the pending rejections.

Firstly, as stated in the previous office action, the Patent Office is a fundamentally different institution from the Food and Drug Administration. The FDA is concerned primarily with the efficacy and safety of new drugs, and makes a judgment based on whether a drug is safe and effective compared to the current standard of care. The Patent and

Trademark Office, by contrast, is concerned with whether a claimed invention represents a novel and non-obvious discovery over the prior art. In order to be regarded as enabled a reference (for example Chappell et al.) must merely describe a process that one skilled in the art could carry out with a reasonable expectation of success. The fact that, for all practical purposes, FDA regulations and malpractice lawsuits would make it impossible to carry out the method in actual clinical practice today does not remove the reference as prior art. It merely indicates that the prior art method is one which the medical profession has decided not to utilize because other therapies, such as antidepressant monotherapy, are judged to be preferable given current priorities.

#XVIII of reply to the 4th OA:

The PTO examiners are making statements that word by word may be factual, and in the semantic of the sentence may appear logical, but it is taken out of the context of the reply: The point is that the PTO examiners disregard that if a method is perceived by the medical profession as such that the skilled in the art that cannot use it for the purpose of our claims because there is a strong teaching against and that there are divergent clinical guidelines, then this should be the PTO's concern in evaluating the applicant's claims. These facts talk against obviousness. The facts are secondary factors. The PTO should be concerned whith that! So brushing off the presented facts and the applicant's proofs about the examinershaving presented an unconvincing line of reasoning is very much inappropriate! The examiners make it appear that the applicant has no knowledge on the difference between the PTO's; the FDA's and the medical practitioners' concern in regards who would find e.g. the Chappell's method suitable for the purpose of our claims. The fact is that the PTO should be concerned with the same issue as the FDA and the medical practitioners and this is why the language used for patentability and obviousness is determined by what the skilled in the art would have done at the time of the invention. So the statements made by the examiners (at p. 29 of the 4th OA) are incorrect and false.

Similarly, the PTO examiners' last sentence on that page is also misleading:

> "The fact that, for all practical purposes, FDA regulations and malpractice lawsuits would make it impossible to carry out the method in actual clinical practice today does not remove the reference as prior art."

The semantic of this sentence may also appear logical, but the overall message is incorrect. The important part is that that the skilled in the art needed to overcome

obstacles in order to practice the invention for the purposes of our claims. The Chappell reference for example did not allow this. This is similar to the fusion nuclear reactor example, that just because it was suggested in prior art that this could be a source of energy; but nobody could carry out building such a reactor as the nuclear plant would have exploded. Therefore in either example it was not possible for the skilled in the art to practice the invention, and if the invention in either case is enabled, overcoming said obstacles it becomes patentable (provided that that field is not banned from patentability due to international agreement).
In addition, it is not the prior art that needs to be removed but the rejection based on prior art, if the prior art does not directed toward solving the same problem; if it is not enabled; or if no obviousness arises. Language is a powerful tool, it should be applied correctly otherwise it can be misleading and falsely convincing. The examiners' following statement has the same conceptual problem.

> "In order to be regarded as enabled a reference (for example Chappell et al.) must merely describe a process that one skilled in the art could carry out with a reasonable expectation of success."

The problem is that there was not "a reasonable expectation of success". It was the examiner and not the skilled in the art or not the prior art who came up with unconvincing line of reasoning – The secondary factors also attest to that effect that the examiners also ignored.

The examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references" if the PTO assumes in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

There are important factors to consider as regards to the prior art like the differences in the function of the invention (In re Ellis, 476 F.2d 1370, [C.C.P.A. 1978].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223). Our claims are aiming a diferent patient population and a new use.

The skilled in the art would be discouraged in following the path (that the PTO recommends) or would lead in a direction divergent from the path that was taken by this applicant. (In re Gurley, 27 F.3.d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224).

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

All these regulations were written down in the replies to the 2nd and other OAs, but the examiners did not find it worthy to read them or to give any feedback to the applicant on the validity of these rules that were taken from self-help patent books written by patent attorneys.

(From p. 30-31 of 4th OA):

Secondly, routine modification of the prior art, or choosing from various options presented in the prior art, is not in itself patentable. Most clinicians would choose to give a depressed patient a single antidepressant as initial therapy, in order to minimize the risk of side effects. Applicant would choose to give the patient an antidepressant plus an antipsychotic, in order to minimize the risk of suicide. Both approaches can draw support from the prior art, although the FDA and most malpractice juries would side with the monotherapy. If the claimed invention is merely a routine modification of the prior art, involving the manipulation of routine result-effective parameters such as dosage level, route of administration, or timing of administration, or the combination of two or more prior art inventions known to be useful for the same purpose or otherwise compatible, the invention is *prima facie* obvious. The patentability of **a *prima facie* obvious invention** depends on the presence of secondary considerations, most notably any surprising or unexpected results stemming from Applicant's modification of the prior art. According to MPEP 2145:

> **Rebuttal evidence** may include evidence of "secondary considerations," such as "commercial success, **long felt but unsolved needs**, [and] **failure of others**." Graham v. John Deere Co., 383 U.S. at 17, 148 USPQ at 467. See also, e.g., In re Piasecki, 745 F.2d 1468, 1473, 223 USPQ 785, 788 (Fed. Cir. 1984) (commercial success). Rebuttal evidence may also include evidence that the **claimed invention yields unexpectedly improved properties or properties not present in the prior art**. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. Dillon, 919 F.2d at 692-93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. In re

Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)

For example, the discovery that administering two agents together produces a synergistic effect with more than additive results, could possible overcome a case of *prima* facie obviousness. In the instant case, Applicant has repeatedly asserted that the combination of an antidepressant and an antipsychotic is especially effective at reducing the risk of suicide. **If this effect is an unexpected result over the prior art, Applicant must provide evidence of this effect in order for it to be considered as a secondary factor affecting patentability**. The specification as originally filed has no evidence of any **experimental** results. Note that further data can be submitted in a declaration under 37 CFR 1.132 in order to establish secondary considerations.

#XIX of reply to the 4th OA:
Similar conceptual problems with the examiners statement continue. The examiners' OA gives the illusion of a convincing logic if only a small part of the facts and regulations are taken into consideration; and only if the text as is written by the examiners appear to be out of context. If we analyze of what the examiners are saying the incorrectness of the logic becomes apparent:

> "routine modification of the prior art, or choosing from various options presented in the prior art, is not in itself patentable"

The present invention is not a routine modification. In fact as we described it gives a solution of a long felt unsolved need that saves lives. If it would have been a mere "routine modification or a choice from various options" the skilled in the art would have used it long ago. The FDA directors would have not embarrassed themselves in prime time and front page interviews with their inability to give a solution to the problem solved by the applicant. In fact the paradoxical effect of the antidepressants causing suicide and the FDA's black box warning has gotten attention in every media prime coverage, but without a solution. This has happened years after the application. So the examiners should not downplay the invention as they did, calling it "as routine modification" and "prima facie obvious". It is of note that with the exception to the last OA when only one of the many secondary factors were acknowledged, the examiners ignored the detailed reply and facts that the applicant presented about these secondary factors. The applicant has even enclosed attachments about the secondary factors. In fact it was impossible to miss these parts as cut outs from front page interviews on the FDA directors' inability to solve the problem addressed by the invention were pasted into the reply, and huge font

emphasis was used in the applicant's reply to address concerns that the examiners have dismissed. The second part of the above sentence is equally incorrect and misleading. If it would have been a mere option of choosing this method things may be different. The fact is that obstacles had to be overcame, against strong teaching against; and against divergent clinical guidelines. So the way the examiners had phrased their reply - coupled with the other concerns on the tactics they used - is misleading and puts the invention out of context.

> ***"Most clinicians would choose to give a depressed patient a single antidepressant as initial therapy, in order to minimize the risk of side effects."***

The examiners again are misleading with the above statement. **The PTO has failed to show** that any of the clinicians have acted the same way as the method and with a satisfactory reason or enablement for their action. The impression is **as if** the PTO had already presented the fact for the few exception from most clinician already practicing our method at the time of the invention. In addition, **isn't the criteria for patentability is of what would have been obvious for the average skilled in the art? Isn't the average skilled in the art represents "most clinicians"? The PTO admits lack of obviousness with their statement – if correctly analyzed – whyle still rejecting our claims!** The fact remains that the examiners could not pull a single prior art document to show support that the average skilled in the art would have have the same reasoning then the PTO's. **The PTO only made unconvincing line of reasoning against what the secondary factors showed**. So the PTO ignored these factors, but relied on their false reasoning as if it would be factual and recognized by the average skilled in the art. So the examiners are misleading with their out of context remarks and with their poor imitation of them summarizing the invention.

> "Both approaches can draw support from the prior art, although the FDA and most malpractice juries would side with the monotherapy."

The same problem continues with the examiners' above statement. It gives the impression as if both approaches were carried out before the invention and as if both draw support from prior art before the invention. The examiners' such presupposition is false, and they failed to provide evidence that the skilled in the art would have been in possession of the invention, or even that they would have found that obvious. The presented secondary factors – with the additional weight of a huge liability by many entities even for staying silent had been already presented before.

> "If the claimed invention is merely a routine modification of the prior art, involving the manipulation of routine result-effective parameters such as dosage level, route of administration, or timing of administration, or the combination of two or more prior art inventions known to be useful for the same purpose or otherwise compatible, the invention is prima facie obvious."

We have already discussed part of this sentence that is repeated by the examiners above. The examiners are conditioning the sentence, but with that are also implying that all these would be true for the present invention, when in fact this is absolutely false, and an incorrect statement. In fact the examiners have failed to show that this would be the case. We have discussed above that the invention is not a routine modification or manipulation of parameters, specifically the initial treatment that is crucial to save lives. None of the prior art inventions were known to be useful for the same purpose! The examiners are making a false statement! None of the prior

art references were enabled for the purposes of our claims! The secondary factors show that the skilled in the art would have not copied or relied on the examiners numerous unconvincing line of reasoning. The PTO examiners dealt with this "problem" by disregarding the secondary factors, and disregarding cited PTO rules that if a prior art is not enabling and is not addressing the same problem as the invention the rejection must be withdrawn.

The examiners then state:

> "The patentability **of a prima facie obvious invention** depends on the presence of secondary considerations, most notably any surprising or unexpected results stemming from Applicant's modification of the prior art."

The semantic problem is with this statement that **no prima facie obviousness** existed in the first place!!!!!
The secondary factors testify in that regard! The examiners and only the examiners came to the false conclusion of the alleged prima facie obviousness and could do that only with the unconvincing lines of reasoning that they repeatedly came up with; and by disregarding the applicant's reply; and by using the above discussed pseudo-scientific techniques.
Since **no prima facie obviousness** existed in the first place, no rebuttal evidence is needed! However, clear evidence was presented for failure of others, as the newspaper clips on the FDA directors inability to solve the problem was presented. That was not a speculation but a clear evidence! The cited rule by the examiners did not say that the evidence must be experimental.
Never the less the "invention yields unexpectedly improved properties or properties not present in the prior art". If properties were present in prior art or if prior art would have aimed to solve the same problem as the invention no novelty and no invention would have been present.
We have shown enablement to our invention and of how the unexpected results would be achieved, e.g. by showing how the compounds act on "extended depressive symptoms" and how the psychological; pharmacological and neuroplasticity effects interact. We have presented evidence to these, and not theoretical speculations.

The cited rule by the examiners did not say that the evidence must be experimental. We have discussed that the small entity applicant has no financial means for expensive experiments, and that what is required for a patent is enablement, coupled with the conclusions drawn; not the experiments. We have also drawn analogy before that there may be inventions (like on going to Mars or to a different galaxy) for which providing experiments would be beyond the financial means of even many nations. The PTO did not dispute this.
Therefore what the examiners state: "The specification as originally filed has no evidence of any experimental results." – is irrelevant in this case. Let us repeat **no prima facie obviousness** existed in the first place. The secondary factors are supportive of **that** statement.

> It is of note – as a side note - that it is concerning to the applicant if the examiners want to "checkmark" experiments, and if they are not capable of applying the regulations for patentability in absence of experiments. Moreover, this "demanding for an experiment" is also concerning as we

have shown numerous issued patents that were accepted even when said "experiment" was done but was irrelevant (at least to some of the approved claims). In some instances a language was used by big pharma about these "experiments" suggesting of the inclusion of a group that was not present in the experimental group. The PTO in these cases; for these big entities; was not concerned apparently to the irrelevant nature of these experiments as long as an experiment was done. At least as the presented evidence on procedural matters #11) points to this direction.

(From p. 31 of 4th OA):

Thirdly, a characteristic that is **inherent** in a particular invention, for example the effect produced by administering a particular compound to a particular subject, does not render a claim patentable over the prior art. See ***Ex parte Novitski*** 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Note that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not make the claim patentable. See ***In re Best,*** 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also ***Eli Lilly and Co. v. Barr Laboratories Inc***. 251 F3c. 955; 58 USPQ2d 18691881 (Fed. Cir. 2001) with regard to inherency as it relates to the claimed invention herein. The fact that the claims recite specific motives (e.g. resisting suicide, delaying relapse, avoiding sensitizing a patient to depression) does not serve to differentiate the claims from the prior at **unless** these motives are **manifest in an actual difference in the way the method is performed as compared to the prior art.**

#XX of reply to the 4th OA:

As we stated under #VIII **on alleged inherency:**

"...the PTO examiners only made a statement without explanation on the alleged inherency. Please explain to me the PTO examiners false logic. If an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression, and/or there is a tolerance developed for the antidepressant, how can our claims be inherent for "inhibiting the development of tolerance toward an antidepressant", "avoiding worsening of the depression [that is caused by the antidepressant

itself]"?

Similarly we have shown that depression and suicide is not necessarily correlate, and that you can resolve the suicidality in an instant when the depression persists. [see what we said about Victor Franckle]. Therefore resisting suicide, avoiding suicidal ideation is not inherent. In addition - as we said above - when an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression and causing suicidal ideation and suicide, then how can our method of administering our treatment in our claim be inherent?
The examiners just grouped things together and used a "reject one reject all" principle (see objection under procedural matters #9 above).
Delaying or resisting relapse when there is a factor that tolerance may develop toward the antidepressant or that the antidepressant may paradoxically worsen the depression in no way should be considered "inherent", or the examiners should come up with some type of explanation for how can all these happen."

Therefore the examiners statement s are misleading suggesting an alleged inherency, when the PTO never addressed and explained with any clear and convincing line of reasoning that this would be so and that their statement would be true. The quoted law cannot apply when the conditions – that **is inherency** – is not present. (e.g. claim 116).

A) The **paradoxical effect of antidepressants causing depression and suicide** is solved by our method and the PTO did not explain any convincing logic of how that could be inherent, (nor did the PTO show that prior art was solving the same).
B) If tolerance can develop with antidepressants and antidepressants can cause a worsening of depression (related to the paradoxical effect above) the **avoiding or delaying relapse** cannot be said to be inherent either. If the PTO thinks so the PTO needs to present prior art or a clear and convincing reason to explain that this would be obvious or inherent for the presented method. The PTO has failed to do so.
C) **Cognitive distortion** is also not inherent as we have shown, and the PTO did not present a convincing line of reasoning that it would be so.
D) **Resisting suicide** is also not inherent as depression and suicidal ideation not necessarily correlate, as we have shown e.g. at p.62-66 of our reply to the first OA. In addition our invention with the initial treatment – that is crucial - is different from prior art.
D) Using our method for smoking cessation is also not inherent.
E) Using our method for **resisting suicide** in non-psychotic and non-depressed patients (a) having **cognitive distortions** with functional impairment or health hazards and (b) of a patient **undergoing smoking cessation** is specifically not inherent for our new claim.
F) Using our method for **resisting suicide in a non-psychotic patient suffering from Depression Not Otherwise Specified**, is also specifically not inherent for our new claim.

The examiner must be specific with each of the alleged "inherency" and explain it with clear and convincing logic not just a mere statement that is not substantiated

by any reality based logic.

Furthermore the examiners are downplaying our **new use** to mere "motivations".

> "The fact that the claims recite specific motives (e.g. resisting suicide, delaying relapse, avoiding sensitizing a patient to depression) does not serve to differentiate the claims from the prior at **unless** these motives are **manifest in an actual difference in the way the method is performed as compared to the prior art**."

The PTO should be familiar with the difference of our method with prior art, and that there was substantial difference on "how the method is performed" between the two. The initial treatment and overcoming a barrier in order to able to perform the method is an example, not to mention that prior art was not enabled for the purpose of our claims. The problems our method is solving is also different from prior art.

(From p. 32 of 4th OA):

Rejection of claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 95-103, and 126 under 35 USC 112, first paragraph

Applicant has amended these claims to recite certain specific **functionally defined groups of antidepressants**. However, the problem with the enablement of these classes of drugs is not overcome by the amendment. Essentially, the lack of enablement for functionally-defined groupings of compounds stems from the fact that these groups are open-ended and contain a wide variety of structurally unrelated compounds. Any attempt by one skilled in the art to practice the full scope of the invention would require one to make and test a huge number of compounds that are not yet known in the chemical literature. In fact, for most chemical compounds, it is not known whether they are serotonin reuptake inhibitors, serotonin agonists, NMDA receptor antagonists, etc. Therefore it would be necessary to obtain all of these compounds, either by synthesizing them or by isolating them from a natural source. Either manner of obtaining them would present an undue burden of

unpredictable experimentation. In general, this problem exists for any class of compounds that is defined by its function rather than its structure. In order for one skilled in the art to be able to obtain a representative sample of the full scope of the claimed class, the class of compounds must be recognized in the art as being associated with a particular structural limitation. (e.g. benzodiazepines) The claims as currently amended do not fulfill this requirement. Therefore the rejection is maintained. If Applicant believes the current functional language is acceptable, he should present evidence that one skilled in the art would regard each of the claimed classes as being limited to particular structural features.

#XXI of reply to the 4th OA:

We have discussed this in details under **#V of reply to the 4th OA:**

Please also see the facts presented under #11A, and in particular #11Aa) - #11Ak) above with the corresponding vast number of issued US patents using the same terms that the examiners are declaring would make our claims not enabled thus rejecting our claims.

(From p. 33-34 of 4th OA):

Rejection of claim 65 under 35 USC 112, first paragraph

Applicant argues that the medicinal effect of fruit and fruit juice is the same. By way of rebuttal, two references are presented (Whfoods, American Academy of Pediatrics, particularly p. 1211, left column "Juice in the Food Guide Pyramid," and p. 1212, left column "Conclusions," references included with P10-892) indicating that fruit juice cannot replace whole fruit in the diet, and that fruit juice lacks the nutrients, such as fiber and water-soluble vitamins, that are found in whole fruit. It

is also noted that the metabolism of drugs is expected to be a much more complicated process than the squeezing and juicing of fruit, and to therefore be all the more complex and unpredictable. Because each product is transformed in a way that would affect its suitability for its intended purpose it cannot be regarded as being identical to the unprocessed product.

Applicant further argues that the finding of additional advantages and secondary factors would serve to grant patent protection to a hypothetical future inventor who actually discovers an active metabolite of risperidone, thus preserving the incentive for future research in this area, and that the Office's alleged concern for said incentives is inconsistent with the alleged lack of concern for the incentives involved with the present invention. However, the discussion of the amount of research performed by drug companies on prodrugs was not presented in order to argue that drug companies need intellectual property incentives to perform such research. Rather it was presented in order to demonstrate that prodrugs are not identical to their active metabolites, as if this were the case most pharmaceutical companies would be wasting significant resources to discover a new compound that is exactly identical to an old compound. The entire field of prodrug research is based on the fact that a prodrug is not the same as the active metabolite and that administering one is not the same as administering the other.

The written description standard requires that every element of the claims be described in the specification as originally filed in such a way as to indicate that Applicant was in possession of the claimed invention with all the claim limitations. The specification as originally filed does not describe the active metabolite of risperidone, or active metabolites in general. Therefore this claim lacks written description in the specification. Furthermore, even if correct, Applicant's arguments would not render the invention patentable. Given the

absence of any new teaching in the specification on this active metabolite, even if the active metabolite of risperidone were shown to be substantially identical to risperidone, then any mention of risperidone in the prior art would inherently be prior art against the claimed invention. If making and using an active metabolite were a simple, predictable, trivial modification of a parent compound, then this claim would be obvious over prior art methods involving risperidone. The reason that these rejections were not made is because risperidone and its active metabolite are not in fact identical.

For these reasons the rejection is maintained.

#XXII of reply to the 4th OA:
As we have said it before if the other claims are approved it would be not worth for us further argument on this issue.
However, the examiners are making a logical error with their argument.
Please remember our analogy that if a grape has a medicinal effect then if someone finds that grape juice would have also the same class of medicinal purpose that would be inherent. So if risperidone has an antipsychotic effect the active metabolite is inherent the same way as grape to grape juice (with swallowing the first the second is present).
The examiners are making an argument the other way around therefore it is not relevant, and the presented articles by the PTO is also not relevant in deciding on this issue. The examiners are bringing up the example of prodrug, but an active metabolite at least in this case is not the same as a prodrug, therefore we do not see relevance to the prodrug. We are also referring back to our earlier replies.

(From p. 35 of 4th OA):

Rejection of claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, and 126-130 under 35 USC 103(a) as being obvious over Chappell et al.

Applicant argues that dopamine D4 receptor antagonists are not necessarily

antipsychotic drugs, and presents the Kramer reference to demonstrate this fact. However, Chappell et al. lists an extensive number of specific dopamine D4 antagonists that can be used in this invention, some of which are unquestionably antipsychotics.

For example, p. 20, paragraph 0445 of Chappell *et* al. cites the compound PNU-96415E and incorporates by reference the disclosure of Tang et al. (Reference included with PTO-892) Tang et al. discloses that this compound demonstrates antipsychotic activity in an accepted animal model of psychosis. (p. 442, right column, p. 443, left column) Furthermore paragraph 0446 of Chappell et al. lists olanzapine, which is admitted by Applicant to be an antipsychotic agent. Other D4 receptor antagonists that are recited by Chappell et al. and which are antipsychotic agents include the compounds of US patents 5883094 (see column 4 lines 5-10 of 5883094) 5432177 (column 1 lines 50-59) and 5633376 (column 3 lines 28-38) for example. Therefore Chappell et al. specifically discloses dopamine D4 receptor antagonists that are in fact antipsychotic agents.

#XXIII of reply to the 4th OA:
We refer back to **#VII** of reply to the 4th OA in particular to the following part: "The PTO disregarded our prior argument on D-4 receptors and the lack of enablement in prior art. The PTO examiners are making their rejection basically repeating their unconvincing line of reasoning from the prior OA. To avoid increasing disorganization in the correspondence, we hereby link what the PTO has said here with their later note at page 35 of the 4th OA. However, the PTO examiners have still failed to sufficiently address the applicant's reply to the 3rd OA in particular III/1 and III/9 p.(18-43). Therefore the PTO examiners' statement remains unconvincing. We have cited documentation that the mere D4 activity does not ensure antipsychotic action! Just because some agent showed antipsychotic activity in animal models as the Krammer reference attest to that it does not prove antipsychotic action. Just because Chappell recited the antipsychotic olanzapine as D4 receptor antagonist, this is not an assurance that the antipsychotic action of olanzapine would be due to the D4 activity. In fact it is highly likely that if the D4 receptor would be blocked in an experiment with another agent (not having an agonist or antagonist effect on that receptor) olanzapine would still have its antipsychotic effect (e.g. through the D2 receptor). The PTO disregarded the

applicant's more detailed argument from the reply to the 3rd OA (p.18-43). The PTO did not show that what percentage of the olanzapine's action would be due to the D4 activity – if any, and if that a lone would be sufficient for an antipsychotic action compared to placebo!

It is of note that the historical speculation that the atypical feature of an antipsychotic would be linked to the D4 receptor was not proven and that idea was abandoned.

The fact that Chappell abandoned his application and did not provide enablement for his mere suggestions makes the lack of enablement even stronger. The PTO examiners have repeatedly ignored the cited law of (e.g. p 36 of reply to the 3rd OA):

> **In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."**
>
> **"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public**, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

(From p. 35-36 of 4th OA):

Applicant further claims that treatment of anxiety is different from treatment of . cognitive disorders. However, while factors other than cognitive distortions are involved in anxiety, cognitive distortions are an important and essential part of anxiety disorders. In support of this conclusion, Applicant makes the assertion that anxiety in certain circumstances, such as a totalitarian society or a dysfunctional work environment, is a rational response involving no disordered cognition. However, anxiety in the sense used in the Chappell et al. reference clearly refers to **pathological** anxiety disorders and not to a healthy response to stressful situations. P. 1, paragraph 0010 of Chappell et al. lists specific instances of anxiety as including, "anxiety **disorders,** such as panic **disorder,** with or without **agoraphobia,** agoraphobia without history of panic disorder, specific **phobias,"** and so on. The very fact that the reference is concerned with

a therapeutic method indicates that the conditions being treated are pathological conditions. Otherwise no therapeutic solution would be needed. Thus the instances of anxiety described by Chappell et al. are clearly pathological anxiety disorders and not ordinary stress.

#XXIV of reply to the 4th OA:

The PTO examiners are making a number of errors also reflecting that they are nt familiar with te field and likely did not even read the applicant's submitted material that describes the factors the examiners lacking a knowledge of:

First, the following statement is misleading and the applicant never claimed that, it is a misquote:

> "Applicant further claims that treatment of anxiety is different from treatment of cognitive disorders."

Cognitive disorders and cognitive distortion is not the same it is so different like an airplane to an office. Cognitive disorders may be mental retardation, a cause of brain injury, even psychosis may have certain aspect of cognitive disorder, and certainly some of the antipsychotic like haloperidol may also cause thought blocking.

Cognitive distortion is something else that we have defined. **The two terms should not be confused!**

We have stated in our prior replies that cause and effect is different from the effect of coexisting factors present and also observed. However that does not mean that the elicited effect (or therapeutic effect) was because a coexisting factor. We could not make it clearer then my medical school's teaching example, that just because one got drunk on alcohol on the rock that does not mean that you can get drunk from ice. The examiners ignored our reply and keep insisting without providing a proof that the prior art would have known that antipsychotics (or the combination of antidepressants and antipsychotics) are producing their effect through eliminating cognitive distortions. Please note that antidepressants were taught in prior art to have their effects through the various neurotharnsmitters. No prior art said that the neurotransmitters would be involved that are in depression, anxiety disorders, phobias, panic, and psychosis, personality disorders, and drug addiction and alcoholism would be the same as involved in cognitive distortions. In fact the neurotransmitter mechanisms are not even the same in these disorders. The examiners are misquoting the applicant, and then show that they do not have a grasp on what cognitive distortion is. The PTO is keeping up with unconvincing line of reasoning. The examiner have shown an improvement in the understanding of cognitive distortion as presented in the last OA. However, it is of note that they enclosed a summary paper in support of their line of reasoning for claim rejection and that paper(s) is not a prior ar. Thus that is not a proper ground for rejection – even if all other conditions would have been met.

> The PTO said: "while factors other than cognitive distortions are involved in anxiety, cognitive distortions are an important and essential part of anxiety disorders":

The examiner's above statement is an example to the fact that just because a factor is involved in a disorder, the PTO still have to show that the therapeutic effect of the compound of the invention would have been effected in an obvious manner known by prior art or the skilled in the art. Neither was presented by the examiners, and their line of reasoning was not convincing as said above.

> The PTO said: "Applicant makes the assertion that anxiety in certain circumstances, such as a totalitarian society or a dysfunctional work environment, is a rational response involving no disordered cognition. However, anxiety in the sense used in the Chappell et al. reference clearly refers to pathological anxiety disorders and not to a healthy response to stressful situations. The very fact that the reference is concerned with a therapeutic method indicates that the conditions being treated are pathological conditions. Otherwise no therapeutic solution would be needed."

The examiners seem not be aware of the applicant's writing on the neuroplasticity model, of how pharmacological, psychological [and even gene expression] is interrelated. That part of the applicant's submitted writing was also related to the Stanford prison experiment, and showed that reaction is the same as in a pathological mental disorder; and depression can be elicited in normal subjects. Therefore the "rational response" – as the PTO misinterpreted – becomes the pathological condition. Note that any adverse event can elicit this not just adverse work environment. In fact I believe that exposing this applicant to the degree of adversities with the "tactics" objected under procedural matters and discussed at the first part of the petition can be similar to the adverse effect of the Stanford prison experiment. (Note that the applicant have not signed any papers to be part of any experiment, and any such experiment would be against the declaration of Helsinki on human rights. The "experiments" in the reality shows (with observable reactions – that is eliciting a reaction and testing it by observation) as discussed in the applicant's other pending application may in fact viaolate the declaration of Helsinki.)

The "disordered cognition" is not the same as cognitive disorder. The PTO's statement that "Otherwise no therapeutic solution would be needed" also shows that they have no grasp on the clinical aspect of the art.

(From p. 36-37 of 4th OA):

Furthermore, the references Casey et al., Ost et al. and Uhlenhuth et al. (included with PTO-892) disclose that anxiety disorders, panic disorders, and claustrophobia involve significant contributions from a disordered or abnomial

cognitive style characteristic of anxious or phobic individuals. For example the survey items in appendix A of Uhlenhuth et al., which are used to diagnose a characteristic anxiety-prone cognitive style, includes questions regarding perceptions of positive and negative events, and the importance a patient attaches to future worries. The anxious cognitive style described by this reference fits within the definition of cognitive distortion as including such features as " overgeneralization, all or nothing (always-never) thinking, discounting positives or negatives, blaming and "labeling", assumptions and predictions, and emotional reasoning, all of which lead to "jumping to conclusions", without analysis of the facts," as described in the specification, p. 15, lines 9-13. Furthermore the reference Sharp et al., included by Applicant with PTO-1449 discloses that cognitive behavioral therapy improved the symptoms of panic disorder. Because CBT is focused on correcting cognitive distortions, its effectiveness indicates that cognitive distortions are present in panic disorder. For these reasons the pathological anxiety and panic disorders described by Chappell et al. are seen to involve cognitive distortions. Note that the term "cognitive distortion" even taken in its specific clinical definition, is rather broad and many if not most psychiatric disorders involve some sort of distorted cognition.

With regard to Applicant's reference to the previous equation of depression with cognitive distortion being withdrawn, this argument is not persuasive in view of the cited prior art, namely the presence of distorted cognitive style in patients suffering from anxiety disorder and the effectiveness of cognitive behavioral therapy in reducing the symptoms of anxiety disorder.

#XXV of reply to the 4th OA:

This is related to the previous section, and need to be referred there for a full understanding of this reply here. In particular please note:
"We have stated in our prior replies that cause and effect is different from the effect of coexisting factors present and also observed. However that does not mean that the elicited effect (or therapeutic effect) was because a coexisting factor. We could not make it clearer then my medical school's teaching example, that just because one got drunk on alcohol on the rock that does not mean that you can get drunk from ice. The examiners ignored our reply and keep insisting without providing a proof that the prior art would have known that antipsychotics (or the combination of antidepressants and antipsychotics) are producing their effect through eliminating cognitive distortions. Please note that antidepressants were taught in prior art to have their effects through the various neurotharnsmitters. No prior art said that the neurotransmitters would be involved that are in depression, anxiety disorders, phobias, panic, and psychosis, personality disorders, and drug addiction and alcoholism would be the same as involved in cognitive distortions. In fact the neurotransmitter mechanisms are not even the same in these disorders. The examiners are misquoting the applicant, and then show that they do not have a grasp on what cognitive distortion is. The PTO is keeping up with unconvincing line of reasoning. The examiner has shown an improvement in the understanding of cognitive distortion as presented in the last OA. However, it is of note that they enclosed a summary paper in support of their line of reasoning for claim rejection and that paper(s) is not a prior ar. Thus that is not a proper ground for rejection – even if all other conditions would have been met."

Note that the cited reference is – to my recollection – is not a prior art reference therefore basing the rejection on that is technically improper.

> PTO said: "With regard to Applicant's reference to the previous equation of depression with cognitive distortion being withdrawn, this argument <u>is not persuasive</u> in view of the cited prior art, namely the presence of distorted cognitive style in patients suffering from anxiety disorder and the effectiveness of cognitive behavioral therapy in reducing the symptoms of anxiety disorder."

The PTO is merely making a statement on the applicant's prior reply: with the reference provided is "not persuasive" The rejection is based on an unconvincing line of reasoning and the approach is pseudo-scientific. Namely an observed association or symptom and a cause and effect relationship in regards to the medication specifically targeting and or resolving the condition is two different issues. Depression can be elicited in many ways even pharmacologically. There are many target points in the neurotransmission for the depression. Yet the depressive feeling as end result is the same. The pseudo-logic of the examiners – in the exact same analogy - is that if one medication affects a neurotransmitter then all other antidepressant must effect the same. This statement is far from the truth.
(See also the "getting drunk from the ice in the drink" example). The PTO has disregarded our reply, and also ignored to respond to this specific teaching example.

Our replies to prior OAs should be pertinent and applied herein.

(From p. 37 of 4th OA):
Applicant further argues that the prior art does not disclose any pharmacological treatment of cognitive distortions. The prior art includes many instances in which antipsychotic medication is used to treat disorders such as anxiety, schizophrenia, or obsessive compulsive disorder, that include distorted cognition as part of their pathology. According to MPEP 2145, Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) The fact that Applicant has concluded that antipsychotic drugs act to remove disordered cognition when administered for treating depression, anxiety, or the like does not constitute a patentable invention.

#XXVI of reply to the 4th OA:
PTO said: "The prior art includes many instances in which antipsychotic medication is used to treat disorders such as anxiety, schizophrenia, or obsessive compulsive disorder, that include distorted cognition as part of their pathology."
The problem is with the knowledge base of the examiners, as distorted cognition is not the same as cognitive distortion. The examiner may have read articles that distorted cognition is treated with antipsychotics in schizophrenia but this is not relevant to our invention as the examiners are mixing up terms. Therefore basing the rejection on that is improper.
Therefore the quoted PTO rule was also incorrectly applied.
Furthermore, the following statement by the PTO was also incorrect:

> "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention".

Our invention regarding cognitive distortion was not a "Mere recognition of latent properties in the prior art" and it was not "an otherwise known invention".

(From p. 38 of 4th OA):
Still further, Applicant argues that the fact that cognitive behavioral therapy

combined with pharmacotherapy yields a benefit over CBT alone is persuasive to show that anxiety disorders are not equivalent to cognitive distortions. Firstly, no treatment is 100% effective. Because of this it is reasonable to expect that even patients undergoing CBT will have some residual cognitive distortion and anxiety that would be further corrected by pharmacotherapy. Secondly, it is not necessary to show that anxiety and cognitive distortion are 100% identical, merely that disordered cognition is one component of anxiety disorders.

#XXVII of reply to the 4th OA:
As regards to the first sentence I do not remember saying this, it may be a misquote, or the examiners' simplification.
Then the PTO continues:
"it is reasonable to expect that even patients undergoing CBT will have some residual cognitive distortion and anxiety that would be further corrected by pharmacotherapy. Secondly, it is not necessary to show that anxiety and cognitive distortion are 100% identical, merely that disordered cognition is one component of anxiety disorders."
The problem with this statement is that semantically it may show some logic, but it is not a convincing line of reasoning as this is not what the PTO was expected to show. What was needed for the PTO to show was that the pharmacotherapy (the antipsychotics) were known in prior art to target cognitive distortion, but the examiners failed to provide that prior art reference. The line of reasoning presented by the examiners were equally not convincing as proven in the above previous sections of our reply. Thus in lack of a convincing line of reasoning for obviousness and in lack of prior art addressing to solve the same problem the rejection must be withdrawn. (Rules in this regard were referenced earlier).

(From p. 38-39 of 4th OA):

Applicant also argues that there is a difference between the obvious prior art practice of administering a drug as soon as it is indicated and the claimed practice of administering the drug as initial therapy or as soon as possible. First, the phrase, **"as soon as possible" is a broad limitation** that encompasses a

treatment algorithm whereby treatment is given as soon as indicated. It is not possible under such an algorithm to administer treatment before it is indicated. Because Applicant does not specify what sort of possibility is meant by "as soon as possible" this limitation is so broad as not to meaningfully limit the claim.

Secondly, **the fact that practitioners in the art regard a specific invention (administering the therapy as described by Chappell et al. as an initial therapy) to be inferior to another therapy does not render it patentable.** It is clear from the disclosure of **Chappell et al. that administering a combination therapy for depression gives an added benefit over administering a monotherapy, otherwise the reference would not recommend administering an additional drug when an antidepressant alone would be just as effective.** Those of ordinary skill in the art generally avoid doing so anyway because of the side effects of antipsychotic drugs, but are in fact aware that this option exists in theory.

#XXVIII of reply to the 4th OA:

There seems to be a logical problem with each of the above statements made by the examiner, that requires an analysis for the proper message:
First the ""as soon as possible" is a broad limitation" is incorrect as other limitations were in place that set the exact parameters for the meaning of this description that the skilled in the art would have no problem understanding. Please remember, that our claims are for non-treatment resistant depression and we have defined this in the body of the specification. So the as soon as possible and initial treatment emphasized the treatment being given at the beginning rather then at the end of the specified period. That period therefore is very specifically and clearly circumscribed. So the above declaration by the PTO examiners is false and not true!!!
The fact is that we have also given examples in our description e.g. that the patient may need to be persuaded for the treatment, and that we cannot give medication against the patients' will. The availability of the medication depending the setting of the patient being seen may be another factor that the skilled in the art would understood. So this limitation is not broad as it is further limited with the definition of non-treatment resistance and thus it is meaningfully limiting the claim.

We have discussed that before that the deciding factor is not that practitioners would decide that one method would be inferior to others, but that Chappell's method was not enabled for initial treatment and for the purposes of our claims. There is also a difference if one method is inferior, but still an acceptable option to be used for the purpose intended, and if the other method is perceived that it cannot be used. There were obstacles to overcome and additional steps required and convincing reasons (enablement) to overcome the strong teaching against and divergent clinical guidelines. So the speculations by the examiners are misleading as for the deciding factor for patentability.
The examiners following statement is also misleading as it is presupposing that Chappell made it clear to use combination treatment for the purposes of our claims and **this presupposition only comes from the examiners and it is false!**
Moreover the PTO implying "that option"; that is our method would be "theoretically available" (implied) from the Chappell method; or that being the same as ours - is also incorrect; and it is a misleading statement.
It is not a permissible technique for the examiners to keep stating the above misquotes and non-supported unconvincing lines of reasoning especially after our replies and quoting the PTO regulations in this regard.
We have made reference above of why the rejection must be withdrawn in regards of the Chappell reference that was not enabled and was not directed to solve the same problem.
Furthermore the examiners introduce an implication with their expression as if our method would be an algorithm – and please note that algorithms are not patentable.
It seems that the examiners are seting the emotional stage by carefully using words that by implication would be detrimental to the applicant. The evaluation must be based on facts and facts presented in the reply cannot be disregarded.

(From p. 39 of 4th OA):

Applicant further argues that the differences in doses between the claimed invention and the prior art are crucial to the function of the invention. How is the difference in dose crucial? Applicant has cited no evidence that combining an antidepressant and an antipsychotic allows the antipsychotic to be administered at a lower dosage. In fact, no experimental data is presented at all that would designate this variable as being crucial.

#XXIX of reply to the 4th OA:
We have presented in the body of our specification as well as in our replies that why the low dose is crucial, and that the antipsychotics are also known to have depressogenic (depression causing) properties. That is also true for risperidone that

is an atypical antipsychotic. So I'm puzzled by the examiner's statement of perplexing of how the dose is crucial and not reading our replies.
Note that evidence does not have to be experimental (to be done by the applicant).
Supportive evidence to the above factors had been provided (including for risperidone and the depressogenic effect).

(From p. 39 of 4th OA):

Applicant further argues that the claimed invention involves a new risk-benefit analysis that is not known in the prior art. However, the specification as originally filed does not discuss any risk-benefit analysis or give any evidence that this is the crux of the invention. Rather the specification merely states (without any evidence other than the prior art) that an antidepressant and an antipsychotic can be co-administered in order to reduce the risk of suicide in patients suffering from depression. The extent of Applicant's new cost-benefit analysis appears to be that the risk of suicide is so great that an aggressive treatment including an antipsychotic treatment is warranted in any case of depression even in light of the side effects of antipsychotic drugs. This is not an invention, it is a judgment call. As has been stated before, the mere fact that the invention is regarded by those of ordinary skill in the art as inferior to another approach does not render it non-obvious.

#XXX of reply to the 4th OA:
The PTO makes incorrect statements again, showing evidence for not reading the application:

"the specification as originally filed does not discuss any risk-benefit analysis"

Please see amendment to the specification in reply to the 2nd OA p.110. second section of that page as an example:

> "With this we are involving them in the decision-making, but we are supposed to discuss with them the *risks/benefits,* side effects of the medications, and *available alternatives* anyway. ...
>
> In psychiatry we are not afraid of prescribing more than one medications to

our patients, and the treatment of depression should not be an exception. The treatment of depression can be started right away with more than just one medication, the antidepressant."

Please also see amendment to the specification in reply to the 2nd OA p.111-112 as additional example also the basis of claims 140, 143 that the examiners said had no basis in the specification and would be considered new matter. (That conclusion is also incorrect):

"We have to balance the risk / benefit of our intervention both for the individual patient and for the group of patients we are treating. This had been customary for long, in the medical practice. A good example for this is of how we were treating appendicitis. If the patient showed some typical symptoms that he or she *might* have appendicitis (specifically if the WBC was also elevated), then the surgeon was operating on. The surgeon had rather operated on healthy people for whom it turned out on the operating table that they did not had an infected appendix, (taking out the appendix anyway), then wait until it became obvious that the appendix had perforated. This is quite a standard procedure that surgeons followed. The risk of dying from the operation (without an infected appendix) was far less compared to waiting and having the (high) risk of death from operating late with a perforated appendix.

The clinicians have a responsibility of not only weighting the risk of the individual but also the risk of a group.

We are following similar procedures and we give thiamin routinely for everybody in the emergency room before giving IV glucose, (therefore preventing Korsakov's syndrome in alcoholics). We are routinely testing for drug screen in the ER (and the patient gets charged for the cost); even when the patient says that he or she is absolutely not taking any illicit drugs. This is a standard procedure and good clinical practice. The risk of being operated on or getting a blood or urine drug screen is not the same. Nevertheless, we take into account the risk/benefit for a group not just for an individual. So why are we not more vigorous in preventing suicide? We are not saying that we should blindfoldedly prescribe a combination of psychotropic medication for every depressed person against their will, but to discuss the *risks / benefits* and *alternatives* with the patients as we mentioned it above. It is fortunate, that in this case, with the medication combination we are not only targeting the reduction of suicide (for the individual and for the group as a whole) but other benefits as well, such as a more rapid resolution of the depressive symptoms, the reduction of anxiety, and even a higher response rate (in %) to the treatment. (One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'. This speculation is probably correct, but by itself would not substantiate the added risk using the neuroleptics. With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and

reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor. The other added benefits from the medication combination like the "immediate" response, the decrease of anxiety, or a higher response rate as for the whole group are only secondary. ..."

"It had been noted that in assessing suicide the focus should be on the characteristics of those who commit suicide rather than on the characteristics of patients with suicidal ideation. (Forster P., 1994.) The same article also notes that major depression is associated with the largest number of completed suicide and half or more of all who commit suicide qualify for this diagnosis. About 15% to 20% of all patients with serious affective disorder will kill themselves. (Forster P., 1994.).

On the other hand 8% of borderline personality disorder (BPD) patients will commit suicide. (Forster P., 1994. – cit#21.). BPD is a separate diagnostic category from major depressive disorder and not even listed under the mood disorder category (See DSM-IV-TR.). It is also known that in treating borderline personality disorder (BPD), we are using "all of the available psychotropic medications, and combinations of them". (See also Gabard's video 9/11/1992, – and published by APAin 1995, Markovitz, P. J. et al. 1991, **versus patent** # 5,589,512 on BPD filed January 1994,). It is true, depression is only one of the comorbid conditions associated with BPD, some others being rejection sensitivity and cognitive distortions to the extent of "mini psychosis" (See also Gabard's video 9/11/1992, – and published by APA 1995). (For diagnostic criteria please refer to DSM-IV TR.)
Our point is that with this disorder we were not afraid of using the combination of antidepressants with antipsychotic medications or even adding a mood stabilizer. Yet in major depressive disorder; in serious affective disorder *with 2-2 ½ times more risk for committed suicide*, we continue to refrain from using or even trying this combination. In BPD at times we are even using clozapine (Clozaril) despite for its high risk for agranulocytosis and despite that it had been prohibitively costly, due to the need of weekly or biweekly blood draws (Frankenburg, et al. 1993). We are not recommending Clozaril to treat major depression or other depressive disorders, ... when other much safer (and cheaper) atypical antipsychotic medications are now on the market. However, we do advocate taking a closer look, and considering using the "new generation atypical neuroleptics" or the even newer "dopamine system stabilizers" together with the antidepressants.

What is deceptive at the first look is, that patients with BPD may show more frequent suicidal gestures and may struggle with almost constant suicidal ideation, but the fact remains that the risk of committing suicide is still 2-2 ½ times more in people with serious affective disorder then in BPD. [For the

statistics of suicide risk, please see: (Forster P., 1994.)]

For us in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer atypical antipsychotics."

The PTO than said: "the specification merely states (without any evidence other than the prior art) that an antidepressant and an antipsychotic can be co-administered in order to reduce the risk of suicide in patients suffering from depression."

This above statement contains of incorrect and misleading parts: The "merely states" is incorrect as quite voluminous information from many different sources were brought together as evidence for support of our conclusions that nobody in prior art done before. Bringing information from prior art does not ban patentability. In fact if more then two or three prior art is relied on – or in our case much more then that – that is also considered a secondary factor supporting patentability. So even if the PTO examiners' remark sounds derogatory, it is in fact supportive of the patentability, but in no way bans the issuing of a patent.

The examiners then continue:

"The extent of Applicant's new cost-benefit analysis appears to be that the risk of suicide is so great that an aggressive treatment including an antipsychotic treatment is warranted in any case of depression even in light of the side effects of antipsychotic drugs."

The examiners then continue with an erroneous conclusion:

"This is not an invention, it is a judgment call."

The examiners are taking their conclusions out of the context of the application. This is not a judgement call, it is the result of a conclusion and several steps used to overcome barriers that the skilled in the art and prior art was not able to solve. This provided a long felt unsolved need. This result was made possible by overcoming strong teaching against, and deviating clinical guidelines. This was done through several inventive steps that others did not realize.

Any invention can be downgraded to a "judgment call", including Edison's light bulb: You just have to use the right elements and make a "judgment call" on which elements to use. The sentence semantically seems logical but as you can see with this analogy the logic that the PTO examiners are using over and over along with the said pseudo-scientific tactics" is a powerful but non-convincing line of reasoning.

The next sentence by the PTO was addressed before it is basically a repetition for their false reasoning: "As has been stated before, the mere fact that the invention is regarded by those of ordinary skill in the art as inferior to another approach does not render it non-obvious."

It is not the "inferior" nature for the other methods that we are asking for a patent, but on the true inventive nature, and the inability for the prior art to enable our method and to solve the same needs and problems with the method of our claims.

(From p. 39-41 of 4th OA):

Applicant's arguments appear to stand on two assertions - that the **Chappell** et al. reference **fails to provide enablement** for treating depression because one of ordinary skill in the art would regard administering an antipsychotic to a non-psychotic depressed patient who had not shown resistance to antidepressants as **malpractice**, and secondly that the fact that Applicant's method is undertaken for the purpose of reducing the risk of suicide according to a **cost benefit analysis** that rates the cost of suicide more highly than the prior art cost benefit analysis.

As regards the first assertion, **it has been repeated that just because practicing an invention would be unethical, illegal,** prohibitively expensive, **risky,** immoral, or otherwise undesirable **does not mean that it cannot be patented, or cannot serve as prior art** during patent prosecution. The enforcement of such considerations is left up to other agencies. Otherwise the enablement and non-obviousness of an invention would depend on the regulatory and liability environment at the time. Furthermore, **as** Applicant has provided no additional evidence or data concerning the claimed method beyond what is known in the prior art, **this assertion amounts to saying that coadministering these two agents is malpractice when someone else does it but is not malpractice when Applicant does it.**

As regards the second assertion, the **invention as claimed does not disclose any cost benefit analysis**. The claims do not contain a cost benefit analysis. The **only mention of cost benefit analysis is in Applicant's arguments during prosecution** in an attempt to differentiate the claimed invention from the prior

art. One of ordinary skill in the art reading the instant disclosure would have no idea that he is supposed to undertake a specialized cost benefit analysis in order to justify the claimed invention. In fact, **there is no way for Applicant to know whether the attorney prosecuting the Chappell et al. patent did not make an identical argument concerning the risk of suicide during the prosecution of said application**. Arguments made during prosecution do not constitute a feature of the claimed invention if they are not included as claim limitations. Thus **if practicing the invention of Chappell et al. is malpractice then practicing the present invention is malpractice as well** since one of ordinary skill in the art reading the instant claims would not be directed to undertake any cost-benefit analysis. Therefore this so-called feature does not serve to distinguish the invention from the prior art.

#XXXI of reply to the 4th OA:
As we have said under 8g/F1 and 8g/F2 the applicant himself is tiring out from the PTO examiners throwing unconvincing lines of reasoning in so many counts. The reader may be also at a point of "giving up" and psychologically accepting these false reasons as true rather then taking the effort to analyze of what was really said:

Indeed Chappell fails to provide enablement for the purposes of our claims.

The PTO continues:
"it has been repeated that just because practicing an invention would be unethical, illegal, prohibitively expensive, risky, immoral, or otherwise undesirable does not mean that it cannot be patented, or cannot serve as prior art". "The enforcement of such considerations is left up to other agencies".
Please note that prior art including Chappell reference did not address the same problems and same solutions then the applicant's method. It was the PTO examiners who came up with an unconvincing line of reasoning of why the skilled in the art would have found the Chappell reference obvious. **When we show** to the PTO in our prior replies that **they had an unconvincing line of reasoning**, and when we show that why the skilled in the art – in lack of enablement in the Chappell reference – could not overcome the barriers of applying our method, that is the barriers of strong teaching against and divergent clinical guidelines; **the**

response from the PTO is that this is none of their concern! Now please tell me what type of logic is that? This is absurd!
The PTO must either come up with referencing that prior art is teaching the same as our method along with that that prior art reference must be also enabled, or the PTO must come up with a convincing line of reasoning of why it would have been obvious for the skilled in the art to use our method. We have provided references to the PTO regulation before that if these conditions are not met, the rejection must be withdrawn.
Instead the PTO is ignoring all what we have said (including the cited regulations), **and basically says "their reasoning may not be convincing, but they do not care about that – that is up to the regulatory and other agencies".** Let me say it in other ways: We show that the PTO reasoning was not convincing and that the skilled in the art had an obstacle to overcome, and could not perform the method, and the PTO says that is none of their concern, they – but not the skilled in the art - still find the invention obvious. The requirement is not what the PTO feels now for obviousness, but what the skilled in the art does at the time of the invention.
Of course, let us repeat that the **PTO ignored the secondary factors showing that the invention was not obvious for the skilled in the art**!
It is frustrating to deal with such unconvincing off reality based reasoning. Yes, I said off reality based reasoning as the presented facts and secondary factors were ignored by the PTO examiners!

The following statement is also misleading and lacks a reasonable logic:

> "Applicant has provided no additional evidence or data concerning the claimed method beyond what is known in the prior art,..."

As we have shown before reliance on prior art does not exclude patentability, in fact if numerous prior art needed for coming to the conclusion that can support patentability as a secondary factor.
The PTO continues with the second part of the above sentence:

> "this assertion amounts to saying that coadministering these two agents is malpractice when someone else does it but is not malpractice when Applicant does it."

The examiners just do not grasp the risk management concept that is part of the everyday clinical practice. If you have an obstacle to overcome you cannot do the method. If you or in this case the applicant provides a solution with certain steps to overcome said barrier, then the barrier no longer exist! If the barrier was overcome there is no reasonable risk for malpractice! It is not that there is no malpractice if the applicant does it, there is no malpractice if the previous barriers had been successfully removed and if the method is enabled! That's it! This is quite simple. We gave the analogy of the nuclear plant generated by fusion energy. It was said that theoretically this would be possible, but nobody could practice it as the plant would have exploded! The barrier needs to be overcome and that requires steps, and inventive steps are patentable – maybe with the exception of nuclear energy. I think the PTO examiners should be aware of these rudimentary patent principles, and they should be familiar with the field they are assigned to. It seems that that is not the case with these examiners. This is a serious hardship for the applicant putting him in many ways into adverse situation.

Under #XXX of reply to the 4th OA above we have provided evidence that the specification does indeed has the basis for risk/benefit analysis. Claims 140 and 143 for example do contain said risk/benefit analysis. Therefore the following statement by the examiners is again incorrect and false:

> "As regards the second assertion, the invention as claimed does not disclose any cost benefit analysis. The claims do not contain a cost benefit analysis."

The following statement by the examiners is also incorrect for the same reason:

> "The only mention of cost benefit analysis is in Applicant's arguments during prosecution"

This is continued by another false statement by the PTO but it is so evident that for the sake of time we will skip the analysis.

The PTO examiners are inappropriately putting the burden of proof to the applicant:

> "there is no way for Applicant to know whether the attorney prosecuting the Chappell et al. patent did not make an identical argument concerning the risk of suicide during the prosecution of said application."

This is irrelevant in this context. The regulation requires that there must be a published prior art disclosing statements that is the basis of obviousness, thus the PTO must come forward if indeed the attorney for Chappell had made an identical argument. Whether that would be considered a prior art since it was not published is another question. The PTO did not come forward with any evidence for obviousness for our claims.

The PTO examiners continue with erroneous arguments:

According to the knowledge of the applicant in reading several self-help patent books and having long conversations with patent attorneys when he still had that option in the past, the PTO's statement is incorrect:

> "Arguments made during prosecution do not constitute a feature of the claimed invention if they are not included as claim limitations. "

First of all we have shown that the risk benefit analysis was not done during the prosecution but was in the provisional application and was re-entered into the specification in the reply to the 2nd OA. Second guidance in the specification is a feature, and definitions too should be preferably in the specification and not in the claims. Really, the PTO's statement seems to be misleading, or at the best it is not clear. The continuation of the sentence linking it with a "thus" make no sense as an argument:

> "Thus if practicing the invention of Chappell et al. is malpractice then practicing the present invention is malpractice as well since one of ordinary skill in the art reading the instant claims would not be directed to undertake any cost-benefit analysis."

We have shown above that the PTO seems not to grasp this "malpractice" issue, but the rest of the reasoning is also not logical since guidance and enablement was given in the specification, so the skilled in the art should know exactly for why the method is now enabled, and why the obstacles, and previous teaching against, and the divergent clinical guidelines had been overcome. In addition claims like 140, and 143 is specifically built in the risk/benefit analysis. These are not new claims they were there before the current OA, so the examiners should have been familiar

with them.

(From p. 41 of 4th OA):

Note that any attempt to introduce a cost-benefit analysis into the claims, as is the case with new claims **140, 141, or 143, would be rejected** under 35 USC 112 **as introducing new matter** into the disclosure and lacking written description ins the specification as originally filed, Because the cost-benefit analysis is not described in the claims.

#XXXII of reply to the 4th OA:
(see also #II of reply to the 4th OA)

#XXX and XXXI of reply to the 4th OA above dealt with this issue, providing proof that the PTO examiners did not read the applicant replies and the specification.
The said claims were drawn basically word by word from the specification that was reintroduced at the reply of the 2nd OA.

(From p. 41-42 of 4th OA):

In sum, **the only** "teaching against" practicing the invention of Chappell et al. in a manner that renders the claimed invention obvious is the fact that the current state of the art strongly considers monotherapy to be a better approach as initial therapy. **In theory, the only thing keeping one of ordinary skill** in the art from using combination therapy **is the collective judgment of those in the art** that any improved efficacy is not worth the increased side effects. One of ordinary skill in the art would have various reasons to use the combination therapy of Chappell et al., for example **if the patient were immanently suicidal or expressed a**

strong desire to get better as soon as possible even given the risks of antipsychotic drugs, or if the practitioner were concerned that he case of depression may turn out to be refractory to monotherapy.

#XXXIII of reply to the 4th OA:

The PTO examiners are making their own summary **of their** understanding:

> "the only "teaching against" practicing the invention of Chappell et al. in a manner that renders the claimed invention obvious is the fact that the current state of the art strongly considers monotherapy to be a better approach as initial therapy."

Please not that that too is incorrect and we have provided several other reasons for the strong teaching against in our utility application. (e.g.: p.2:

> "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression".
>
> "it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)"
> "In contrast to antidepressants, antipsychotics alone (including the atypical antipsychotic risperidone) were ineffective in the chronic mild stress (CMS) model (animal simulation of depression) (Papp, M. et al 1996; Papp, M. et al 2000). In sum, many studies showed that antipsychotics do not have significant antidepressant activity and, if anything, may cause a depressogenic effect.
> Due to the severe side effect profiles of the traditional antipsychotic drugs, the risks of taking these drugs, in the absence of their specific indications (such as psychosis, severe agitation or anxiety) were believed to be unwarranted by the medical community. (Price, L.H. et al. 2001. p. 207.)"
>
> And from pp2-3:
> "A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987). The combination use of these medications to treat non-treatment resistant, and non-psychotic depression was never recommended. A book chapter reviewing this topic from year 2001 makes the point that "the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,)."

So The examiners are making a misstatement.

The PTO should provide evidence from prior art for obviousness or should provide a convincing line of reasoning. Making theories of what they think the skilled of the art would think – and making this theories against common sense and against the presented facts and secondary reasons – is inappropriate reason for rejecting the claims. Yet the examiners statement refers that they are doing exactly that inappropriate pattern:

> "In theory, the only thing keeping one of ordinary skill in the art from using combination therapy is the collective judgment of those in the art that any improved efficacy is not worth the increased side effects."

The PTO continues with their non-convincing line of reasoning – being blindfolded as they disregard the secondary factors showing of how really the skilled in the art is thinking. The PTO continues:

> "One of ordinary skill in the art would have various reasons to use the combination therapy of Chappell et al.,"

The fact is left out that the skilled in the art was against a barrier, divergent clinical guidelines etc. Sure anybody could have come up with the same reasoning and solution as the applicant, and document this in the patients chart, but the fact remains that they did not – and the secondary factors support that. This false reasoning by the PTO is also true to any invention: If others were thought of the invention first they would have gotten it! Do you see the absurdity of the examiners repeated logic? The examiners continue:

> "for example if the patient were immanently suicidal"

We have presented in the previous replies of what was the procedure for "imminent suicidality" according to the standard treatment preceding the invention. So continuing with this speculation and assuming that this is a convincing line of reasoning is inappropriate. The examiners continue:

> "or expressed a strong desire to get better as soon as possible even given the risks of antipsychotic drugs,"

The examiners keep stating the same false assumption taken from Tollefson, that the combination treatment achieves a faster resolution of depression (taken form the data of treatment resistant depression) then antipsychotic monotherapy alone. We have presented data – actually published by Tollefson himself that antipsychotic monotherapy achieved the antidepressant effect within the same time frame as the combination therapy. So the examiners not only continue with unconvincing lines of reasoning tiring out the applicant and the reader, but also show evidence that they did not read the applicant's replies!

The same is true for the next part of the sentence:

> "or if the practitioner were concerned that he case of depression may turn out to be refractory to monotherapy."

We have presented with the secondary factors plenty of evidence from prior art and even from publications following the application, that the current state of the art and clinical guidelines were teaching against of starting the treatment with anything else then antidepressant monotherapy. So again the examiners are making their rejections when they do not even read the applicant's replies. I do not even mention that the PTO examiners are grossly unfamiliar with the art that they are making judgment on. The data was presented to PTO examiners, but they did not read it and that is making their behavior absolutely unacceptable!!!

(From p. 42-43 of 4th OA):

Applicant further asserts that his own method would not be subject to charges of **malpractice** because of the risk/benefit analysis that he would undertake. Any practitioner would undertake **a** risk/benefit analysis before administering therapy. There is nothing special about Applicant that makes his risk/benefit analyses especially valuable or persuasive. Why has Applicant chosen to second-guess the existing thinking about antipsychotic risks and benefits in depression? Because he believes that the expected benefits are worth the expected risks. **That is a decision, not a discovery, and it does not rise to the level of novelty or unobviousness needed to be patentable**. The fact is, all that separates Applicant's reasoning from the prior art reasoning is that Applicant is more worried about suicide and less worried about tarditive dyskinesia and other side effects. **Any practitioner having the same priorities would come to the same conclusion**. If it would be impossible for one of ordinary skill in the art to practice a combination therapy for treating depression, than it would be impossible for Applicant as well. Both the specification as originally filed and the provisional application 60/319436 rely for their reasoning on a collection of various prior art references on the treatment of depression, the risk of suicide, and the benefit of antipsychotics. Applicant is relying **entirely** on what is known in the prior art about therapy of depression for enablement, and simply coming to the conclusion that there would be a sufficient benefit to aggressively treating depression to warrant using a more aggressive therapy initially. **If Applicant had shown** that the risks of antipsychotics were less than was believed in the prior art, or **that the benefits were greater**, or that **this method were**

unexpectedly effective in reducing suicide among depressed patients,

then this showing might be evidence of secondary consideration.

Otherwise there is no additional element that is not obvious from the prior art.

#XXXIV of reply to the 4th OA:

This is elated and overlaps what was already discussed under #XXXI of reply to the 4th OA.

The examiners are showing that they just do not get the concept of this malpractice issue, that how overcoming an obstacle would change the way the reasoning of the skilled in the art.

> "Applicant further asserts that his own method would not be subject to charges of malpractice because of the risk/benefit analysis that he would undertake. Any practitioner would undertake **a** risk/benefit analysis before administering therapy."

The above is a very judgmental statement from the examiners in particular that as we have shown above that they did not read the replies and the application, and the risk benefit analysis.

There is also a logical error that the examiners are making. Doing the novel risk/benefit analysis of the applicant that overcomes the teaching against, the divergent clinical guidelines, and doing "a" risk benefit analysis that the practitioners were doing before that is one that is different from the applicant's method would result in different outcomes. Yet you have to be attentive that the examiners said "a" risk/benefit analysis. The following statement is devaluing the applicants enabling guidance. Note that the risk/benefit analysis is not the only enablement that the applicant provided, and that showed of why the antipsychotics are useful in the method. **Let's not forget that that just because the examiners have picked one of the many things that was needing for enablement and for overcoming the obstacles of using the method that does not mean that the applicant did not overcome these other barriers that prior art was not able to solve.** So the PTO is stating in focusing only on the risk/benefits:

> "There is nothing special about Applicant that makes his risk/benefit analyses especially valuable or persuasive."

The examiners seem to not to be avare of the risk benefit analysis being part of the specification as we have shown in #XXX above that their comments are revealing this fact. It is not surprising that if the examiners are not aware of what is in the specification then they are not finding that valuable or persuasive.

The fact is that the applicant is even bringing analogy that in other parts of the medical practice we have to take into consideration not only the benefit of the individual but the benefit of the group as well. The applicant was taught to that guideline during his medical school – and he was taught that this is so because the **benefit of the group is also the benefit of the individual. We do not know who in the group would be affected!** The applicant also approaches this from another angle, (bringing the data from many sources) and let me exemplify this a bit more

drastically here: The applicant makes his point that the skilled in the art is without a blink gives all kind of medication combination in case of borderline personality disorder. (The exaggerated message is that if these patients bother the psychiatrists constantly – even in the middle of the night – than the risk of the medications on the patients are of no concern for the psychiatrists. If however the patient is quiet and depressed and has 2-1/2 (two and a half) times more mortality from suicide then the other personality disorder group, then the psychiatrists and clinical guidelines are all yelling out of do not give medication combinations that are risky for the depressed patients, they do not bother us, they just quietly die!) Now, the applicant told in the application that this is not permissible. The two diagnostic category is different, so the applicant also had to enable the method of why the antipsychotic would be useful for the treatment of depression and in particular for the "prevention" of suicide. If you the reader thinks that the skilled in the art should have realized the same as the applicant you are right. However the skilled in the art even years later still did not come to the same conclusion. It is also notable that the applicant had to overcome several, actually too many obstacles to enable the method, so this was not as easy as it sound here.
So is there anything valuable or persuasive in the applicants risk/benefit description? Is the result for the ability of saving more lives then half of the fatalities during the worst infectious epidemic of all times convincing enough for an unexpected result? And this result would be only for the timeframe of this evaluation period so far! Is this convincing enough even if nobody seems to care? The applicant has revealed that he believes that the financial incentives are needed for the "big pharma" to become interested, but that was already mentioned before. So does the PTO seem to be impressed? No the examiners had shown evidence that they did not even read the applicant's reply. The PTO states about the applicant's risk/benefit analysis:

> "That is a decision, not a discovery, and it does not rise to the level of novelty or unobviousness needed to be patentable."

The final step in every invention is a decision, you either use it or not. However the risk benefit analysis is not the invention, this is a step or a series of steps that allows to use of the method, a combination of compounds, and new use. These are all patentable, and as we have shown the invention was not obvious even years later. The secondary factors support that.

The examiners continue with their unconvincing lines of reasoning – in disregarding the secondary factors – the presented facts that contradict the examiners' conclusion:

> "Any practitioner having the same priorities would come to the same conclusion."

The fact is that they should have but they did not!

The examiners then are repeating the same unconvincing line of reasoning not taking into consideration that the barriers not allowing for the use of the method had been overcome by the applicant:

> "If it would be impossible for one of ordinary skill in the art to practice a combination therapy for treating depression, than it would be impossible for Applicant as well."

> "Both the specification as originally filed and the provisional application 60/319436 rely for their reasoning on a collection of various prior art references on the treatment of depression, the risk of suicide, and the benefit of antipsychotics. Applicant is relying entirely on what is known in the prior art about therapy of depression for enablement, and simply coming to the conclusion..."

We have shown before that relying on prior art does not banning patentability. In fact if many prior art needed to come to the right conclusion that is even supportive of the patentability based on secondary factors.

> "If Applicant had shown that the risks of antipsychotics were less than was believed in the prior art, or that the benefits were greater, or that this method were unexpectedly effective in reducing suicide among depressed patients, then this showing might be evidence of secondary consideration."

This had been shown in relying on multiple prior art in enabling that the risk/benefit alternative analysis makes it a treatment of first choice – as that term used in the art and as we have said this in our utility application page 4 on the last but one line.

Most recently a double bind placebo controlled study sponsored by a drug company had shown that unexpected effect. In that study about 6 and a half years later then our priority date the patients in that study had suicidal ideation but the group of patients had treatment resistant depression. (**Reeves H et al Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled study. J. Clin Psychiatry 69:8 August 2008**)
An earlier case study that is not a prior art also showed that all patients in the publication receiving combination treatment stopped having suicidality, and showed improvement. All those patients had resistant depression. (**Viner MW et al Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. Journal of Clinical Psychopharmacology 23:1 2003**).

The PTO's following statement is incorrect. Just because the conclusion had been drawn from prior art, if there is a significant number of prior art (more then three – and in our case much more then that) that can be in support of patentability based on secondary factors:

> "Otherwise there is no additional element that is not obvious from the prior art."

So that statement is incorrect.

(From p. 43-44 of 4th OA):

Applicant further argues that a risk/benefit analysis is patentable, **as**

demonstrated by the instance of clozapine. However, the three PCT international **publications** W096/31621, W09721833, and W097/32037 cited by Applicant are not patents. They are international **applications** filed under the Patent Cooperation Treaty that carry no intellectual property privileges and merely serve as priority documents for national phase applications. Thus their existence proves that someone filed for a patent on a cost/benefit analysis but not that said patent was granted. Note that none of these applications resulted in the grant of a US patent. Also note that assessing a patient's response to a therapy is different from administering the therapy itself, which is what is being claimed in the instant claims. Similarly, the instant claims are not related to a method of ameliorating side effects or monitoring side effects from a therapy, or of specifically administering the therapy to a group of patients who would derive the greatest benefit. It appears that the later patents for clozapine referred to by Applicant are US patents 5563134 and 5312819, (References included with PTO-892) which claim compositions and methods further comprising and **additional** ingredient that ameliorates the adverse effects, and US patent 6197764, which claims a conjugate of clozapine with a fatty acid. Neither of these patent are analogous with the claimed invention as they introduce additional limitations over the prior art, namely modifying the structure of clozapine or adding an additional element to the pharmaceutical formulation. In any case, Applicant has not identified any granted US patent claiming a cost/benefit analysis. Furthermore, note that 3539573 claims priority all the way back to the original invention of Clozapine in Aug. 16, 1960, (thus it is the original Clozapine patent) and 3962248 claims **a** process of making clozapine, and not the compound itself. Furthermore note that at the time 3962248 was issued the patent term in the

US was 17 years from the date of issue, rather than the current term of 20 years from the filing date. Therefore it would have expired on June 8, 1993, 31 years after clozapine was invented. Because of the delay in prosecution that can occur, patents issued during that time period (so-called "submarine" patents) could often have **an** expiration date many decades after their original priority date. Therefore the late expiration of a patent on Clozapine does not prove that the Office issued a second patent on the same medication in view of a new cost-benefit analysis.

#XXXV of reply to the 4th OA:
The PTO examiners present a speculation for "submarine patent" for he clozapine patent in particular by listing 2 patent documents:

3539573 issued Nov 10, 1970 that the PTO says claims priority all the way back to the original invention of Clozapine in Aug. 16, 1960; and
3962248 was issued June 8 1976 (and the PTO says the patent term in the US was 17 years from the date of issue. Therefore it would have expired on June 8, 1993, 31 years after clozapine was invented.

(see also #III/13 p 30-36 with the attached articles in the reply to the 3rd OA):
However the PTO disregards the presented documentations (Stoner; Paton) that showed that the clozapine patent monopoly actually expired 37 years (not 31) after the discovery of the drug. Therefore the applicant did provide the needed proof (even if not with a patent number but with publications stating the patent expiration day). The applicant did that along with his explanation of historical data that the drug company did claim inventive steps similar to the risk/benefit steps for the current invention.

In addition the examiners did not read the applicant's reply carefully as the language he used was more permissive. The issue here is that US patent principles were used – regardless of the patent extension was executed but the PTO or another governmental body authorized to do so. The US patent principles were relied on – hence the proof of the US patent extension that we provided. Therefore the examiners' speculation is an incorrect explanation in comparison to the historical data originated form the drug company on the stepwise inventive steps that through secondary factors overcame obviousness.
Please note that to my recollection about 30% of the schizophrenic patients are treatment resistant and about 1% of the population is affected by the disease. The price tab for the medication is absorbed by the society in large (this is a difference to depression where this is not the case). Therefore clozapine would not qualify to be an "orphan drug", and the data previously presented in the attachment on the market share for the antipsychotics clearly show that this is a "lucrative" business

for the drug companies.

> "Therefore the late expiration of a patent on Clozapine does not prove that the Office issued a second patent on the same medication in view of a new cost-benefit analysis."

The above statement by the PTO examiners therefore is taken out of context of the reply and is incorrect. **The US patent principles were applied to extend the patent for clozapine, and historical data shows that it was because of the stepwise risk/benefit analysis.**

Please also see our summary point under
"The example of the inventive steps leading to clozaril patent monopoly for over 37 years, and the similarities and dissimilarities with our application." shown below p. 160-162.

(From p. 44 of 4th OA):

Applicant further argues that the reasoning used in the rejection would render obvious a (putatively ridiculous) therapy involving 20-30 different medications and anticonvulsant therapy. Such a therapeutic method would in fact probably be considered enabled by the Office. What stops physicians from practicing it is not the disapproval of the USPTO but rather the ordinary and routine cost-benefit analysis performed by any physician before administering a therapy. It is indeed obvious to combine any number of existing therapies **because one of ordinary skill in the art would be able to tell if doing so was warranted and to refrain from doing so if it was not.**

#XXXVI of reply to the 4th OA:
The problem with the above statement by the examiners is that they leave out if there was a true enablement in an application claiming a combination of 20-30 different medication, or if someone just made a mention of "here is a bunch of medicine" and just claiming without enablement (that is without reasoning and proof) that these do work together (or might not). This is why we said that the Chappell reference was not enabling for the purpose of our claims because they just said "use these together" without overcoming the existing obstacles.
So someone submitting "combine the medications from PDR for any and all

diseases" (and not saying why, and how to overcome difficulties) is ridiculous, and even more ridiculous if these PTO examiners [and hopefully not the PTO] would find this enabled!

> "Such a therapeutic method would in fact probably be considered enabled by the Office."

Therefore I cannot believe the above statement by the examiners being true and correct.

Please note that the examiners demanded during the prior office action a very scrutinizing enablement. It does not sound to me that the examiners are asking the same level of scrutiny for enablement from others, even from Chappell, and a mere mentioning to do something is found sufficient for enablement in these other cases.

Most importantly, the "pseudo-logic" used by the examiners is surprising me, that they come up with an unconvincing line of reasoning (of why Chappell would render our invention obvious when it was not obvious for the skilled in the art) and when the examines are confronted with their reasoning not being convincing, they brush off the reply that it is not up to them but to the physician to decide what to use and what would be obvious for the skilled in the art. I thought that the criterion for obviousness is what the skilled in the art would do and not such "wishy-washy unconvincing logic" by the examiners. That is it is not acceptable for the examiners to say that something would be obvious for the skilled in the art, and when it turns out not to be the case, the examiners to say sorry, that is none of our concern but to the skilled in the art to decide of what to use. This is not a convincing line of reasoning at all! And the PTO examiners repeat these reasoning over and over again! I think that pattern needs to stop.

(From p. 45 of 4th OA):

Applicant also argues that various additional properties recited in the claims are not inherent because the prior art did not describe or understand that all of these additional properties were considered inherent. Applicant appears to misunderstand the nature of inherency. It is not necessary that the prior art recognize an inherent property. Rather **all that is necessary is that the prior art teach a method that would in reality possess the claimed effect** whether or not the effect is explicitly disclosed. In the instant case, the prior art describes administering the same two compounds to the same patient population. If the effect exists in the claimed invention it exists fir the prior art method as well,

as the effect of practicing the same method will not depend on whether the practitioner read about it in the Chappell et al. reference or the instant application. This method would inherently produce the claimed results as it is substantially identical to the claimed invention.

#XXXVII of reply to the 4th OA:

The PTO states that:

"Applicant appears to misunderstand the nature of inherency."

"It is not necessary that the prior art recognize an inherent property. Rather all that is necessary is that the prior art teach a method that would in reality possess the claimed effect whether or not the effect is explicitly disclosed."

I think the examiners are the one who are misapplying the rules.

We have said this analogy in our prior reply that just because aspirin is used for fewer or pain using that compound for preventing heart attack and stroke is a new use. Why would new use be patentable if inherency would exclude it from patentability?

The examiners continue to err in their comment for the for the reason that "teaching" by Chappell of just making a mention and not enabling it for the purpose of our claims (or even for their claim since they abandoned their application) is not considered a "teaching". If the skilled in the art cannot use it because to overcome of the obstacles and teaching against is not explained, then it is not a "teaching". Therefore **no inherency** can possibly present for a method that the skilled in the art is not using for the same patient population described in our method!

"In the instant case, the prior art describes administering the same two compounds to the same patient population.

If the effect exists in the claimed invention it exists for the prior art method as well, as the effect of practicing the same method will not depend on whether the practitioner read about it in the Chappell et al. reference or the instant application. This method would inherently produce the claimed results as it is substantially identical to the claimed invention."

The prior art did not practice the method of the claimed invention. So the PTO examiners assumption for "effect exists in the claimed invention it exists for the prior art method" is incorrect and not a convincing line of reasoning!

Therefore it appears that the examiners are the one misunderstanding and misapplying the inherency, not the applicant.

Furthermore the examiners did miss answering to what we raised under #VIII above on inherency. (The examiners did not have a chance to read this prior of this reply but they could have read the application and claims and not to jump in their reject one reject all conclusions):

"Also the PTO examiners only made a statement without explanation

on the alleged inherency. Please explain to me the PTO examiners false logic: If an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression, and/or there is a tolerance developed for the antidepressant, how can our claims be inherent for "inhibiting the development of tolerance toward an antidepressant", "avoiding worsening of the depression [that is caused by the antidepressant itself]"?

Similarly we have shown that depression and suicide is not necessarily correlate, and that you can resolve the suicidality in an instant when the depression persists. [see what we said about Victor Franckle]. Therefore resisting suicide, avoiding suicidal ideation is not inherent. In addition - as we said above - when an antidepressant is expected to improve the depression, but it exhibits a paradoxical effect of causing depression and causing suicidal ideation and suicide, then how can our method of administering our treatment in our claim be inherent? The examiners just grouped things together and used a "reject one reject all" principle (see objection under procedural matters #9 above). Delaying or resisting relapse - when there is a factor that tolerance may develop toward the antidepressant or that the antidepressant may paradoxically worsen the depression - in no way should be considered "inherent", or the examiners should come up with some type of explanation for how can all these happen."

Similarly under #XX above we stated:

"Therefore the examiners statements are misleading suggesting an alleged inherency, when the PTO never addressed and explained with any clear and convincing line of reasoning that this would be so and that their statement would be true. The quoted law cannot apply when the conditions – that **is inherency** – is not present. (e.g. claim 116).

A) The **paradoxical effect of antidepressants causing depression and suicide** is solved by our method and the PTO did not explain any convincing logic of how that could be inherent, (nor did the PTO show that prior art was solving the same).

B) If tolerance can develop with antidepressants and antidepressants can cause a worsening of depression (related to the paradoxical effect above) the **avoiding or delaying relapse** cannot be said to be inherent either. If the PTO thinks so the PTO needs to present prior art or a clear and convincing reason to explain that this would be obvious or inherent for the presented method. The PTO has failed to do so.

C) **Cognitive distortion** is also not inherent as we have shown, and the PTO did not present a convincing line of reasoning that it would be so.

D) **Resisting suicide** is also not inherent as depression and suicidal ideation not necessarily correlate, as we have shown e.g. at p.62-66 of our reply to the first OA. In addition our invention with the initial treatment – that is crucial - is different from prior art.

D) Using our method for <u>smoking cessation</u> is also not inherent.

E) Using our method for **resisting suicide** in non-psychotic and non-depressed patients (a) having **cognitive distortions** with functional

impairment or health hazards and (b) of a patient **undergoing smoking cessation** is specifically not inherent for our new claim.

F) Using our method for **resisting suicide in a non-psychotic patient suffering from Depression Not Otherwise Specified,** is also specifically not inherent for our new claim.

The examiner must be specific with each of the alleged "inherency" and explain it with clear and convincing logic not just a mere statement that is not substantiated by any reality based logic.

Furthermore the examiners are downplaying our **new use** to mere "motivations".

> "The fact that the claims recite specific motives (e.g. resisting suicide, delaying relapse, avoiding sensitizing a patient to depression) does not serve to differentiate the claims from the prior art **unless** these motives are **manifest in an actual difference in the way the method is performed as compared to the prior art**."

The PTO should be familiar with the difference of our method with prior art, and that there was substantial difference on "how the method is performed" between the two. The initial treatment and overcoming a barrier in order to able to perform the method is an example, not to mention that prior art was not enabled for the purpose of our claims. The problems our method is solving is also different from prior art."

(From p. 45 of 4th OA):

Applicant argues that inherency is disproven by the Simon et al. reference that shows that combining benzodiazepam with an antidepressant does not lead to any reduction in relapse of panic disorder. This argument concerns benzodiazepam which is not a compound used by Chappell et al. or the instant claims. Thus it does not disprove inherency.

#XXXVIII of reply to the 4th OA:

(see #III / 14c) p. 37 of reply to the 3rd OA):

What the applicant said was that the examiners have presented an unconvincing line of reasoning by saying that anxiety and cognitive distortions are the same.

> In "An article by **Simon** they combine benzodiazepam alone antidepressant alone and combination of the two and conclude that the combined pharmacotherapy does not appear to provide greater protection from relapse than monotherapy (see last two lines in the abstract). Although this study is for panic (anxiety) [that the PTO erroneously considered cognitive distortion] it **would argue against that relapse prevention with multiple**

> **medications would be inherent** (and obvious in all cases) – as the PTO stated without evidence. That Simon reference therefore shows that the PTO's line of reasoning was not convincing, it is not necessarily so that combining any two medications would be preventive of relapse. Adding a second medication does not make relapse prevention inherent."

This article is very much pertinent to the subject of alleged inherency, as it shows that combining two medications together that are targeting the same symptoms does not achieve the "inherent benefit –as claimed by the PTO". This is regardless that benzodiazepam is not in the claims of Chappell. The applicant had to prove that the examiners' line of reasoning was unconvincing and he successfully did that.

> "This argument concerns benzodiazepam which is not a compound used by Chappell et al. or the instant claims. Thus it does not disprove inherency."

Therefore it is not appropriate for the examiners when they are confronted with their unconvincing nature of their line of reasoning to brush it off saying the compound is not in Chappell's claims.

This is in addition of what we said under #VII and #XX, #XXIV-XXVI, and #XXXVII above

(From p. 45-46 of 4th OA):

Applicant further argues that using a low dose of antipsychotic agent would not be obvious. However in the absence of unexpected results or other secondary considerations, one of ordinary skill in the art would be able to select an appropriate dosage level from the teaching of the prior art. Note that paragraph 0459 of **Chappell et al. discloses** a dose of about 0.05-1500 mg for the dopamine D4 antagonist and indicates that lower dosages can be used in some circumstances. P. 15, lines 1-2 of the original specification indicates that a low dosage is 25-50 chlorprobazine equivalents, or 100-150mg chlorpromazine equivalents Q.D. Olanzapine, as discussed earlier, is mentioned as **a** dopamine **D4** agonist by Chappell et al. P. 1570 of Merck (of record in previous action) indicates that **4** mg olanzapine is equivalent to 100 mg of chlorpromazine. Therefore 25-50 or 100-150mg chlorpromazine equivalents of olanzapine is about 1-2 or 4-6mg olanzapine, which falls within the general teaching of Chappell et al.

Furthermore Merck discloses (pp. 1568-1570) significant side effects, and further suggests (p. 1571, left column, first paragraph) that for maintenance therapy the lowest dose possible should be administered. In view of these teachings of the prior art, lowering the dose would be seen as a routine modification of the prior art. It is common sense that lower doses of a drug produce less serious side effects and that the minimum effective dose should generally be used for drugs with serious side effects.

#XXXIX of reply to the 4th OA:
The following is in addition of #VII, #XXIII, #XXXIII above.

Please note that Chappell did not enable our method! In fact the Chappell reference was abandoned and never used for the purposes of our claims. That would successfully invalidate the above PTO argument.
As we have said above a "teaching" by Chappell that never overcame the obstacles that would have been necessary for the use of our method, cannot be taken against us.

> **In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."**
>
> **"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public**, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Also:

> Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.**
> If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"
>
> **As we have shown the prior arts cited do not anticipate our claims**
> **We have also shown the secondary factors that the prior art teach away.**

And:

If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

As well as:

The PTO need to present a convincing line of reasoning for obviousness or th rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat Ap & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003
page 219).

In other words the same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J). "that
references must ... suggest [our] claimed invention, or [the] examiner must present a
convincing line of reasoning as to why the artisan would have found [our] claimed invention
to have been obvious in light of the teachings of the references.
(Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." We have shown in our reply that there is no obviousness the prior art is different or not enabled, and the skilled in the art
could not have disregarded the boundaries of standard of care without adequa guidance,
and without going through a risk/benefit/side effect, available alternatives analysis (etc).
We came up with new inventive steps that enabled to use our invention.

In addition the Merk reference for maintenance therapy is concerned with psychosis and not depression.

Furthermore in our previous replies we have given an argument on the low dose and why it would have been a challenge for the skilled in the art to experiment with various doses of antipsychotic medications possibly making the depression worse. Quotations pasted from our utility under #XXXIII especially about depressogenic effect also support our statement that the examiners err with their conclusion that modification of the doses would be routine for the skilled in the art – which in general may be true, but not in a new territory, new use – other then what the antipsychotics were approved for - such as the subject of our invention.

(From p. 46-47 of 4th OA):

Finally, Applicant argues that Chappell et al. does not specifically disclose non-psychotic, non-treatment-resistant depression as a specific category of

depression. However, Chappell et al. discusses depression and psychosis **as** two different categories, and even refers to them in the alternative (depression **and/or** anxiety **and/or** psychosis) in paragraph 0020. As regards non-treatment-resistant depression, one skilled in the art, reading the disclosure of Chappell et al., would interpret it as applying to all types of depression and not just treatment resistant depression. There is nothing about the disclosure of Chappell et al. that would lead one skilled in the art to conclude that the teaching of depression only applies to depression hat is treatment-resistant.

With regard to the rejection over Tollefson et al., this rejection was withdrawn because Tollefson et al. specifically targeted only treatment-resistant depression. Chappell et al. does not limit the disclosure to treatment resistant depression.

#XD of reply to the 4th OA:

We do not argue with the examiners' second sentence as we have said the same. Indeed prior art have used the combination of antidepressants and antipsychotics for psychotic depression (psychosis), and also for ["non-psychotic"] treatment-resistant depression (TRD).

However there is considerable problem with the following statements made by the PTO examiners:

> "one skilled in the art, reading the disclosure of Chappell et al., **would interpret** it as applying to all types of depression and not just treatment resistant depression."

This is an opinion only by the examiners. The examiners could only maintain this opinion by disregarding the facts (previously presented) on secondary factors that even years after the application the skilled in the art acted differently then the presupposition of the examiners. Therefore the examiners were proven wrong.

> "There is nothing about the disclosure of Chappell et al. that would lead one skilled in the art to conclude that the teaching of depression only applies to depression that is treatment-resistant. Chappell et al. does not limit the disclosure to treatment resistant depression."

Now, word by word this may be true, but the skilled in the art does not limit their basis for performing their daily routine on what was published by the PTO. So that is not the Chappell reference that would lead to conclude the skilled in the art to

what to apply for the non-enabled Chappell's statement, but the skilled in the art's general knowledge of what is permissible and what is not at the time of the invention.
Chappell might have not limited the use of his application and there could have been may reason behind this. Not limiting and enabling is two different things. Not limiting and giving sufficient guidance and reasoning of what exactly the method should be used for is also another thing. Therefore the examiners' statement as they phrased it is totally meaningless and irrelevant. The secondary factors also support the applicant that the examiners reasoning is the one that is non-convincing.

(From p. 47 of 4th OA):

To summarize, Applicant's claimed invention is based on practicing a nonpreferred variation of the known prior art, namely administering combination antidepressantlantipsychotic therapy as initial therapy in order to treat depression more aggressively so as to reduce the risk of suicide. **The prior art is aware that combination therapy exists**, but it is not used in actual clinical practice as a first-line treatment because of the side effects of antipsychotics. Applicant argues that it should be used as a front-line therapy because avoiding suicide is more important than avoiding the side effects of antipsychotics. Applicant presents **no evidence** for this proposition, but rather argues based on what is already known in the prior art. The "invention" in this case is merely a shift in priorities from minimizing harm to maximizing benefit. A shift in priorities is not patentable **unless it results in an unexpected benefit.** In the instant case, Applicant does not show any unexpected benefit but rather theorizes that his priorities would lead to fewer suicides **because of less time waiting for a therapeutic benefit.** This is not a sufficient secondary consideration to overcome the ***prima facie*** **case of obviousness.**

For the reasons discussed above, the rejection is deemed to be proper and maintained.

#XDI of reply to the 4th OA:
The examiners start this paragraph to limit the applicant's invention to only one set of claims and ignore the others (e.g. on giving a solution paradoxical effect of antidepressant causing suicide or worsening depression).

Second the PTO's statement for

> "The prior art is aware that combination therapy exists, **but it is not used in actual clinical practice...**"

is important from several standpoint. The first part is misleading, as combination therapy indeed does exist as the applicant also revealed this, but it is for a different patient population. Therefore being "aware" of the combination treatment that is used for something else does not carry an automatic obviousness. This is an important distinction. The second part of this sentence acknowledges that the method is indeed not used in clinical practice. Therefore the **PTO examiners with this are invalidating all their previous statement on what would be obvious by the skilled in the art, and acknowledging that it was not obvious.** The problem is that the examiners are not withdrawing the obvious rejections, but despite of their acknowledgment they maintain the rejections.

The PTO arguments following this is also incorrect as the applicant did present evidence (not experiments) of why would the reduction in suicide occur, and why we should follow the method. The applicant did overcome obstacles that others had inability to solve. Therefore the applicant did much more then a "mere shift in priorities". In addition to the above he also provided detailed guidance and enablement. We have discussed it before that relying on prior art does not ban patentability, and in fact if so many sources needed for the conclusion it may even support the patentability based on secondary factors.

As we said (e.g. p 78 of reply to the third OA):

> "The applicant feels that his invention has a great importance to solve a long felt need, and of saving lives. In fact the method could have been saved up till now up to almost half of the fatalities of the worst (contagious) infectious epidemics of all times in the USA (the fatalities of the 1918 flu)."

I think it is an unexpected benefit.

This however did not occur because of the PTO's reasoning:

> "because of less time waiting for a therapeutic benefit" as the PTO continues with the erroneous conclusion even after it was show to them that the time for the therapeutic effect occurs in the same timeframe with antidepressant monotherapy and the combination treatment.

We have shown that no "prima facie case of obviousness" existed, and the bolded part of the examiners statement (in this box of reply) also points to that fact.

Thus the rejection was not deemed proper.

(From p. 48 of 4th OA):

Rejection of claims 106-108 as obvious over Chappell et al. in view of Berman et al.

Applicant restates arguments applied to Chappell et al. alone and repeats the assertion that he has presented a "vast amount of secondary factors". These arguments are not found persuasive for the same reasons discussed above. No additional arguments are made beyond saying that what has been stated previously applies further to ketamine.

Furthermore, Applicant's use of ketamine is based merely on a couple sentences in the specification that mention ketamine as an antidepressant. Using ketamine is only enabled because of the evidence in the prior art that it is an antidepressant. If the prior art such as Berman et al. is not enabling for the antidepressant effects of ketamine then there would be no basis for Applicant's use of ketamine either.

#XDII of reply to the 4th OA:
Removal of the Chappell reference on the basis of our prior arguments and on the basis that that reference is not enabling would satisfy the requirement to answer the objection in view of Berman.

As regards to the next PTO statement:

> "he has presented a "vast amount of secondary factors". These arguments are not found persuasive for the same reasons discussed above."

I'm puzzled by this statement as the examiners have not addressed the presented secondary factors prior to the 3rd OA, and even then they bulked them together. The PTO ignored that the secondary factors would make the examiners line of reasoning an unconvincing one.
So what I see here is a "brush off" without explanation. The PTO sais these secondary factors were not found persuasive – but really, for what reasons? No discussion by the PTO was done on the unconvincing nature of the presented facts on the secondary factors. In fact, we have presented evidence, not an opinion, or speculation with the publications that continued even after the application and with the front page news reports of leading national newspapers. This does not only

apply to the ketamine but to every aspect of our invention.

In attempting to make their point the examiners are taking things out of context:

> "If the prior art such as Berman et al. is not enabling for the antidepressant effects of ketamine then there would be no basis for Applicant's use of ketamine either."

This is phrased in a twisted way, and this is not relevant. We never said that Berman was not enabling for the antidepressant effect. However, there is a huge difference of applying ketamine for non-treatment resistant depression, or going even further and applying it as initial treatment and of what Berman and other prior art studies have shown. To my recollection all prior art used ketamine for treatment resistant depression only. One would need a darn good reason to use it as initial treatment, and while we have provided such reasons overriding side effects, the prior art at the time of invention, and to my best recollection did not. These are important differences that the PTO cannot ignore. Please refer back also to our prior replies.

(From p. 48 of 4th OA):

Rejection of claims 126-128 as anticipated by Robertson et al.

Applicant argues that anxiety is not a cognitive distortion. This has already been addressed above in the response to the arguments concerning Chappell et al.

Applicant also argues that if Robertson et al. would anticipate the instant claims it would also anticipate the Tollefson et al. patent. The "Tollefson et al. patent" (W099/61027) is not a patent. It is an international application published under the Patent Cooperation Treaty, an international organization outside the jurisdiction of the USPTO. While it could serve as a priority document for a US patent application, it is not itself a patent and never issued as a patent. Therefore it is not relevant to determining the standards used by the USPTO. Furthermore, each case is examined on its own merits. Examination is guided by the patent statute and the Manual of Patent Examination and Procedure (MPEP), not by precedent from earlier cases.

Applicant further argues that Robertson et al. reference has been rendered obsolete by progress in antidepressant therapy. However, a rejection for anticipation under 35 USC 102(b) is a statutory bar and no secondary considerations can serve to overcome it. All that matters is the literal teaching of Robertson et al. **and whether it fall within the limits of the claimed invention**.

As regards claim 126, this claim is no longer rejected on these grounds as amitriptiline is not seen to be included within the scope of claim 126.

As regards inherency, initial treatment, and low dose administration, inherency is discussed previously, and claims 127 and 128 to not require low dose treatment or treatment as initial therapy.

#XDIII of reply to the 4th OA:
The PTO examiners err in their reasoning as it is also reflected by the issued patent for **Tollefson, US6,960,5577,** Combination therapy for the refractory depression.

(Please also note that the examination may be guided by the MPEP but that would not excuse the PTO form under discriminating the applicant especially if a pattern can be demonstrated as we have discussed this under #11 objections under procedural matters.)

We had also addressed our reply under #VIII above on the same topic. Robertson could not anticipate our claims at the time of our invention as Robertson had different type of antidepressants available not the newer kind in our claims. The guidelines also did change with the introduction of the safer antidepressants. Therefore no anticipation could occur with the introduction of new medications and at the time of our invention. Therefore the teaching of Robertson does not fall within the limits of the claimed invention.

The alleged inherency, initial treatment, cognitive distortions, low dose was discussed earlier and sufficient reply given for withdrawal of the rejection.

The paradoxical effect of antidepressants worsening depression and causing suicide, and our method solving this long felt unsolved need was also not anticipated by Robertson, and the PTO left out addressing these set of claims, that should be (also) allowed.

(From p. 49-50 of 4th OA):

Rejection of claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 under 35 USC 103(a) over Chappell et al. in view of Schmidt

Applicant argues that this rejection is overcome by the arguments against the rejection over Chappell et al. alone. These arguments are discussed above.

Rejection of claims 5, 9,16,20, 24,28,64, 75, 79, 83,87, and 125 under 35 USC 103(a) over Chappell et al. in view of Roth

Applicant argues that this rejection is overcome by the arguments against the rejection over Chappell et al. alone. These arguments are discussed above.

#XDIV of reply to the 4th OA:
Please refer to our previous replies above and to earlier OAs.

(From p. 50 of 4th OA):

Rejection of claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, and 129 under 35 USC 103(a) as obvious over Robertson et al. in view of Merck

Applicant argues that if Robertson et al. were prior art the Tollefson et al. "patent" would never have issued. This argument, and other arguments concerning initial treatment, low dosage, and inherency, have been addressed

previously.

Applicant further argues that Robertson et al. has been rendered obsolete by new developments in the field of pharmacotherapy and that one of ordinary skill in the art would not have applied it at the time of the invention. According **to** MPEP 2123, "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, **31** USPQ2d 1130, 1132 (Fed. Cir. 1994) The fact that safer drugs were known at the time **does not mean** that one of ordinary skill in the art **could not have combined** a typical antipsychotic with an antidepressant. It merely means that those at the time of the invention **chose** not to. While this case of *prima farce* obviousness could be overcome by the presentation of concrete data showing some unrealized benefit from combining the two drugs, Applicant has not shown any such benefit.

#XDV of reply to the 4th OA:
This had been discussed under #VIII and #XDIII of reply to the 4th OA:

The PTO examiners err in their reasoning as it is also reflected by the issued patent for **Tollefson, US6,960,5577,** Combination therapy for the refractory depression.

(Please also note that the examination may be guided by the MPEP but that would not excuse the PTO form under discriminating the applicant especially if a patern can be demonstrated as we have discussed this under #11 objections under procedural matters.)

Initial treatment, low dosage, cognitive distortion, solution to the paradoxical effect of antidepressants worsening depression and causing suicide, and inherency, have been addressed previously.

The PTO errs with the conclusion on the issue being the composition found inferior to monotherapy by the skilled in the art, and therefore not using it. The issue was of the skilled in the art encountering an obstacle and not being able to use the method for the patient population of our claims without first finding an enablement, and overcoming said obstacles.

The PTO also errs with the following statement:

> "The fact that safer drugs were known at the time does not **mean that one of ordinary skill in the art could not have combined a typical antipsychotic with an antidepressant**. It merely means that those at the time of the invention chose not to."

Actually, the opposite of the first sentence is true. With the strong teaching against with the divergent clinical guidelines, the "do not harm principle" from the medical doctor's oath the practitioner could not use that combination at the time of the invention for the purpose of our claims. Could not use it unless finding an enablement, that no prior art had shown, and the secondary factors are supportive to that that such enablement by others was not in place. So not choosing it is correct but this is in the context of not being able to, and due to the barrier that needed to be overcome. We have discussed the analogy of the fusion energy nuclear plant before. The engineers there too "choose" of not to use that method because they do not want to explode.

This issue was discussed before.

(From p. 50-51 of 4th OA):

Rejection of claims 106-107 under 35 USC 103(a) as obvious over Robertson et al. in view of Berman et al.

Applicant argues that this rejection is overcome by the arguments against the rejection over Robertson et al. alone. These arguments are discussed above.

#XDVI of reply to the 4th OA:

The answer had been given earlier.

(From p. 51-52 of 4th OA):

Rejection of claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 4143, 48, 49, 51-64, 66, 70- 77, 79-81, 83-85, 87-89, 91-105, 109-122, and 124-129 under 35 USC 103(a) as obvious over Pivac et al. in view of Merck.

Applicant argues that the Ferris et al. reference proves that thinking about

the action of antidepressants needs to be reevaluated, thus casting doubt on the teaching of Pivac et al. about antidepressants. However, Ferris et al. was published in 1983, 19 years before the publication of Pivac et al. and more importantly before the widespread use of SSRIs as antidepressants. The antidepressants discussed by Ferris et al. are other types of antidepressants, such as **MAO** inhibitors. This is shown by the fact that Ferris et al. never mentions serotonin reuptake inhibition or compares bupropion to a serotonin reuptake inhibitor. At the time of publication, zimelidine was the only SSRI available and had just been marketed for about one year. Fluoxetine would not be introduced into the marked for several years yet. Therefore the teaching of Ferris et al. is not seen to contradict or cast doubt on the teaching of Pivac et al. concerning SSRI antidepressants.

Applicant further cites several other references to show uncertainty as to the reasons for the synergistic effects observed between certain antipsychotics and antidepressants. However, uncertainty only overcomes a case of obviousness if it is sufficient to cast into doubt whether there would be any reasonable expectation of success using the invention. Merely showing that the method by which an invention works, as is the case with the Toth, Roth, and Cremers articles, is not fully known does not keep one of ordinary skill in the art from using it. Furthermore, The cited prior art does not show that atypical antipsychotics to not work to augment the effects of antidepressants but merely that they might exert this effect in a different manner than was supposed by Pivac et al. The one reference showing a clear negative teaching, Perez et al., concerns patients with depression **resistant to SSRIs.** Because the claimed invention specifically deals with non-treatment-resistant depression this teaching

that pindolol does not overcome treatment resistance is not relevant to the claims.

The Jordan et al. reference concerns aripiprazole, which has a different method of action from atypical antipsychotics, being a partial agonist of the dopamine receptors. Therefore results concerning aripiprazole are not directly relevant to the atypical antipsychotics which are different molecules with a different receptor profile.

All other arguments made by Applicant have been addressed earlier as applied to other rejections in this action.

#XDVII of reply to the 4th OA:

Detailed reply with reference to the OA's above page number had been provided above under **#XIV** and #XV of reply to the 4th OA.

(From p. 52-53 of 4th OA):

Rejection of claims 1-4,7,8,10-15,19,23,27,31,36-38,41-43,48,49,51-63, 67, 68, 7074,78,82,86,90,95- 105,109-122, and 124-130 under 35 USC 103(a) as obvious over Jordan et al. in view of Merck.

Applicant argues that Ferris et al. shows that it is not known how bupropion affects sensitivity to antidepressants. This is not relevant as the rationale for combining the references is that both drugs are useful individually and thus expected to produce an additive effect when combined. This does not require that the antipsychotic alter sensitivity to the antidepressant. Furthermore as discussed above Ferris et al. was published before the widespread use of SSRI

antidepressants or atypical antipsychotics other than clozapine, and does not concern the compatibility of dopamine system stabilizers such as aripiprazole with **SSRIs.**

Applicant further argues that an analogous compound, busipirone is not approved by the FDA for treating depression and not used off-label for this purpose either. This is not relevant as the standards of patentability used by the PTO are concerned with whether one of ordinary skill in the art **could** practice an invention, not whether those skilled in the art have, collectively, decided not to use a particular therapy as reflected by the decision of the FDA.

. Furthermore, the Landen et al. reference is not persuasive to remove the rejection as it concerns the treatment of refractory depression while the claims are drawn to treatment of non-refractory depression.

All other arguments made by Applicant have been addressed earlier as applied to other rejections in this action.

#XDVIII of reply to the 4th OA:
Detailed reply with reference to the OA's above page number had been provided above under **#XV** (and #XIV) of reply to the 4th OA.

The PTO examiners are repeating their unacceptable pattern of behavior that when they are confronted that they had an unconvincing line of reasoning they brush off the reply that "it is not persuasive" or "not relevant".

> "the Landen et al. reference is not persuasive to remove the rejection as it concerns the treatment of refractory depression while the claims are drawn to treatment of non-refractory depression."

In this case the the Jordan (and Pivac) reference was analyzed in light of the PTO examiners' line of reasoning. Therefore the Landen reference dealing with the exact compound mentioned by the Jordan reference (buspirone) having an agonistic activity at 5-HT1A receptor the same way as disclosed for aripriprazole. Therefore showing that prior art (the Landen reference) showed that it was not more efficacious than placebo, is very much relevant and should be persuasive to show that the examiners did not have a convincing line of reasoning. It is also known by the skilled in the art that buspirone is not useful for the treatment of depression.

See also #X / 2a-2) p. 65 of reply to the 3rd OA.

(From p. 53 of 4th OA):

Rejection of claims 106-108 under 35 USC 103(a) as obvious over Jordan et al. in view of Berman et al.

Applicant argues that this rejection is overcome by the arguments against the rejection over Jordan et al. alone. These arguments are discussed above.

#XDIX of reply to the 4th OA:

The answer had been given earlier.

(From p. 53-54 of 4th OA):

Rejection of claims 3-5, 9-15, 20, 28, 37, and 50-52 under 35 USC 103(a) as obvious over Theobald et al.

Applicant complains that no copy of Theobald et al. was enclosed. Theobald et al. is a US patent pre-grant publication and is publicly available to Applicant from the USPTO. Therefore no copy was enclosed with the rejection. In order to expedite prosecution, copies of Theobald et al. and the prior PCT publication have been enclosed with this office action.

Applicant's further arguments were made without reading the reference and are not found persuasive. Specifically, Theobald et al. is enabling because it does in fact disclose both antidepressants and antipsychotics, as discussed in the body of the rejection.

For these reasons all rejections of record in the previous office action are maintained.

#D of reply to the 4th OA:
Detailed reply had been provided above under **#XVII** of reply to the 4th OA.

The examiners err in deciding what constitutes to enablement similarly to their argument for the Chappell reference without enabling - as that reference was also discussed above

(From p. 54 of 4th OA):

Conclusion

No claims are allowed in this application.

#DI of reply to the 4th OA:
As we have presented the examiners have shown evidence of not reading the applicant's replies and submitted application in full, that they are ignoring presented facts including the erroneous and unconvincing nature of their line of reasoning, the facts about secondary factors and on what the skilled in the art have considered obvious. The examiners also downplayed the applicant's invention, its' value, its novelty and unobviousness, and have put out of context their arguments in rejecting the claims. The examiners have also ignored cited regulations of why the claim rejection must be withdrawn. The examiners have shown evidence of not being knowledgable in the field confusing frequently used terms (like cognitive distortions with cognitive impairment). The examiners also relied on pseudo-scientific techniques as presented under objections on procedural matters. These are only some example without wanting to repeat the all the deficiencies of the examiners. In sum the examiners made inappropriate rejection for the claims.

The following is provided for the Commissioner of Patents (and/or to the new examiners) as a starting point to summarize the differences between the application and prior art.

Please note that new references not previously discussed are included in this part.

Secondary Factors

The following secondary factors support unobviousness of our patent. (We will discuss the secondary factors in more details after this list):

1) Previous failure of others (See e.g. FDA directors' inability to give adequate solution)
2) Solves insoluble problem (See e.g. FDA directors' inability to give adequate solution)
3) The invention is in a crowded art (There are a lot of inventions on antidepressants)
4) Unsuggested modification (e.g. for initial treatment substantially in everybody depressed; treatment of 1st choice; looking the interest of a group; lower dose of antipsychotics; etc)
5) Unappreciated advantage (for the paradoxical effect of antidepressant worsening depression; for the development of tolerance against the antidepressants; for antidepressants causing suicide; prevention, modifying course of illness, SI prevention, etc)
6) Solution of long felt need (not solved by others) (e.g. SI prevention); (See FDA director's inability to give adequate solution; see Tollefson / Eli Lilly and Chappell / Pfizer not recognizing the use for preventing the paradoxical effect of antidepressants worsening depression or causing suicide; and not speaking up in the midst of FDA and media attention.)
7) Contrary to prior art teaching (even in the light of intense media attention, and highly recognized experts like FDA chiefs)
8) Synergism (described in the application)
9) Prior art references would not operate in combination (lower dose of antipsychotic is better; initial treatment for the interest of a group is essential;)
10) References teach away from combining (or its use), (This, in the light of intense media attention makes this factor much stronger! In addition, lack of teaching the same as in our invention (with the details), should be also considered a teaching away in our case, when it would be the legal duty of drug companies to reveal and teach that knowledge – if realized by them – and them not doing so would expose experts like the drug companies and the FDA to significant legal liabilities. The lack of teaching the same as in our invention (with the details) by these experts (FDA and drug companies), would be the violation of the law if indeed they would have come to the same conclusions, or they would anticipate from their prior art the same conclusions that we have made). – In this regard the Genetech factor is also applicable: "Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion.**" And "patent protection is granted in return **for an enabling disclosure of an invention**..."
So, teaching away and lack of teaching the same by others (in intense media and FDA attention), as secondary factors are all supporting the patentability of our invention.
11) Most recently the FDA asked AstraZeneca pharmaceutical company (in approving quetiapine for bipolar depression), that a black box label (about suicidality) be included, for quetiapine an atypical antipsychotic similar to that became a requirement for all SSRI and other antidepressants; therefore teaching against our invention that the antipsychotics would have a protective effect. (The drug company

complied, and I was notified about this by mail in November of 2006. – A copy of this letter and the new labeling information is enclosed for your reference).

Secondary factors
And
Our **specifics of inventive points:**
1; Prevention of suicide with the use of the medication or combination, (low dose antipsychotics), and through initial treatment taking the interest of the group and the individuals
2; Prevention or treatment of the paradoxical effect of antidepressants
3; Prevention of the progression of the disease, modifying the course of the disease.
4; Prevention of relapse.
5; Cognitive distortion
6; Smoking cessation (in non-psychotics) with or without other treatment modalities

	1	2	3	4	5	6
Previous failure of others	yes	yes	yes	yes	Yes	yes
Solves insoluble problem	yes	yes	yes	yes	Yes	yes
The invention is in a crowded art	yes	yes	yes	yes	Yes	yes
Unsuggested modification (e.g. for antidepressants causing suicide; for initial treatment (for most) everybody – as described; lower dose of antipsychotics; etc)	yes	yes	yes	yes	Yes	yes
Unappreciated advantage (prevention, modifying course of illness [being superior than antidepressants alone] etc)	yes	yes	yes	yes	Yes	yes
Solution of long felt need (not solved by others) (e.g. SI prevention)	yes	yes	yes	yes	Yes	yes
Contrary to prior art teaching (even in the light of intense media attention, and highly recognized experts like FDA chief)	yes	yes	yes	yes	Yes	yes
Synergism (described in the application)	yes	yes	yes	yes	Yes	yes
Prior art references would not operate in combination (lower dose of antipsychotic is better)	yes	yes	yes	yes	Yes	yes
References teach away from combining (or its use), (Again this is in the light of intense media attention. Lack of teaching (in addition of teaching away) should be also considered a teaching away in this case when not doing so would expose large entities to significant legal liabilities or would be the violation of the law).	yes	yes	yes	yes	Yes	yes

Secondary factors continued, (discussion and details):

News that appeared after our PTO application about the FDA warning on risk of antidepressants causing suicide had been heavily and repeatedly publicized in virtually all US newspapers and all media.
In the intense FDA, professional and media attention, even up to date, the "obvious conclusions" attempted by some was not followed by the skilled in the art, and many years later, there is still teaching away from our invention. One cannot expect that a good number of leading projects some also sponsored by the NIMH, or from national to international forums, would all teach away (and keep doing it from 2002-2005, or till 2009), if these "conclusions" would be really obvious from prior art as the examiner have repeatedly stated that. In addition all these teaching away were published in leading professional journals. The editors of these journals did not only accepted these teachings against our invention (years later), but did so without even making an editorial comment. With the need of solution (our invention) and that need being in the FDA, professional and media attention one cannot say that others would

come to the same conclusion at the time of our invention, as we did, as one cannot expect that many leading professionals and the FDA, and the NIMH who were sponsoring studies that teach away would be all blind to these facts.
One cannot expect that the directors of the FDA would embarrass themselves in their national front page interview of being perplexed about a lack of solution (on antidepressants causing suicide) and being perplexed of not knowing what to do if they would have recognized our teaching or if the same conclusions would have been "obvious" and could have been drawn from prior art. (Please see the FDA newspaper interview from March 2004 and December 2006 in the enclosure).

Therefore secondary factors strongly oppose the obviousness rejection.

(Please also see these teaching away and references/ publications from 2002-2005 under **Consid: 2) here:**

Consid:2): Teaching away (publications from 2002-2005):
(A,) Texas Algorithm Project, (B,) The Berlin Algorithm Project – and **(C,) The Algorithm Study of the German Research Network on Depression** – and **(D,) the Sequenced Treatment Alternatives to Relive Depression (Star*D)** and NIMH-funded multisite trial – are <u>all teaching away</u>:

Consid: 2)-A: Texas Algorithm is teaching away (see figure 1 of publication in the enclosure.)

Now, we have discussed how important it is to use the risk/benefit (side effect) analysis, in light of alternatives of other strategies for faster (rapid) onset antidepressant action. We have also discussed, and will further elaborate on it below how the FDA and others were teaching away from our method (or not even recognizing our method).

Texas Algorithm is a nationally recognized initiative for giving guidance to different mental illnesses, and as such many US states (about half of them) have adapted the Texas Algorithm. [See e.g. publication by Dewan, N.A. Psychiatric services 2003 Vol 54/12 1646-49 on implementing this in Ohio]. These states made the Texas Algorithm mandatory and to be used in the state psychiatric facilities (including State hospitals). Pennsylvania adapted this under the name of PennMaps. I have received from a pharmacy reminders to use the Texas Algorithm adaptation under PennMaps on community (non-state facility) patient as well. (The adaptation of the Texas Algorithm was done in different stages, starting with the treatment of schizophrenia with plans to follow this mandated protocol for other mental illnesses). We are not focusing here on whether this policy by the states is correct or not, we are simply pointing out of how widely accepted the teaching of the Texas Algorithm is. So, the Texas Algorithm (as referenced below for the treatment of depression [MDD]), is teaching away from our invention not only in regards of "other" fast action antidepressant alternatives, but also as to not to use combination at the beginning of therapy. It teaches away by starting the treatment of depression as monotherapy, and therefore teaching of not to use treatment resistant depression (TRD) methods as initial treatment at all. Actually, it did not even occur to them, that a more vigorous treatment as initial treatment would be useful, for the prevention of suicide. So this is another factor to show, that our methods are not obvious to the skilled in the art.

Their teaching away from our invention, supports the patentability of our claims.

Reference: Tiverdi M.H. et al Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project Arch Gen Psych 2004 Vol 61 669-680.

Consid: 2)-B) and Consid: 2)-C): and Consid: 2)-D): (B,) The Berlin Algorithm Project – and (C,) The Algorithm Study of the German Research Network on Depression – and (D,) the Sequenced Treatment Alternatives to Relive Depression (Star*D) and NIMH-funded multisite trial – are all teaching away:

References:
Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

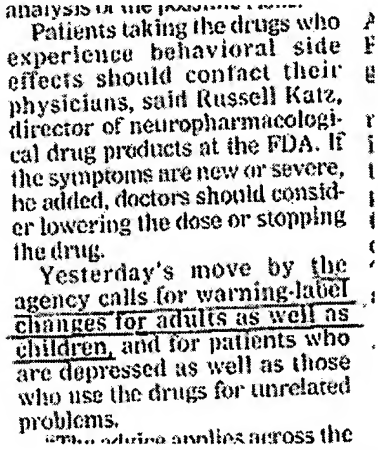
Standardized Stepwise Drug Treatment Regimen (SSTR) – teaching away:

Aldi, M. et al Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: Result of a 2-year observational algorithm study. J Clin Psychiatry 2002, 63:9 782-790.

In addition; Effectiveness study is also teaching away:

Remission rates with 3 consecutive antidepressant trials: Effectiveness for depressed outpatients. J Clin Psychiatry 2005; 66:670-676.

In addition, when the FDA director was interviewed on the new FDA warning on the antidepressants causing suicide, he was teaching away from our invention, suggesting decreasing or stopping the antidepressant (leaving patients having suicidal thought and their doctors with very limited options). This has happened after our patent application. So secondary factors intensely support that prior art did not anticipate our invention, and they were teaching away from it:



analysis of the positive risks.

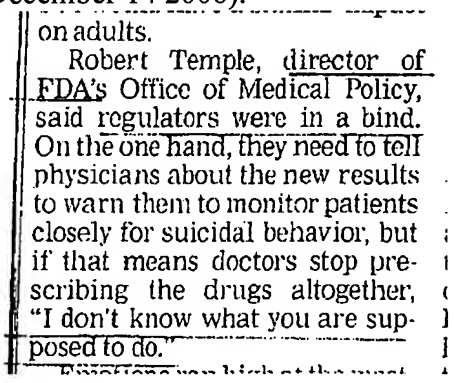
Patients taking the drugs who experience behavioral side effects should contact their physicians, said Russell Katz, director of neuropharmacological drug products at the FDA. If the symptoms are new or severe, he added, doctors should consider lowering the dose or stopping the drug.

Yesterday's move by the agency calls for warning-label changes for adults as well as children, and for patients who are depressed as well as those who use the drugs for unrelated problems.

The advice applies across the

(Please see the FDA directors' statement below and the full article in the enclosure.)

In addition most recreantly this teaching away repeated itself as demonstrated by another front page interview with a different FDA director (December 14 2006).



on adults.

Robert Temple, director of FDA's Office of Medical Policy, said regulators were in a bind. On the one hand, they need to tell physicians about the new results to warn them to monitor patients closely for suicidal behavior, but if that means doctors stop prescribing the drugs altogether, "I don't know what you are supposed to do."

The FDA is perplexed about the lack of solution (and seemingly unaware of our solution or application and PTO publication). (The FDA never contacted us asking for any further information). The FDA director stated that he does not know what he is supposed to do [or suggest].
(Please see the FDA director's statement below and the full article in the enclosure.)

We on the other hand have made an extensive risk/benefit analysis, and have provided enabling guidance. (No matter how convincing or "obvious" it sounds now – our teaching was not recognized by prior art). [In fact our guidance is still not being recognized about 4 ½ (or 6 ½) years later, despite all of the intense media and FDA attention on this subject].

Furthermore, major pharmaceutical companies could be hold legally liable of not being forthcoming to the regulatory agency and the public with a solution if indeed they would have concluded the same as we did in our application. (The same liability may apply for the FDA). (Some of these major pharmaceutical companies were even cited by the examiner e.g. in the Tollefson, reference). **So before anyone would say that our invention is obvious, or even that our reasoning and reply to the 1st office action is obvious from the prior art, one should consider the vast amount of secondary factors we have listed here.** The final proof is not that our invention should have been anticipated, but whether it was at the time of the invention. As the secondary factors show, this was not the case, and therefore these secondary factors support the novelty and unobviousness of our invention.

Additionally , Tollefson had been actively involved (with his studies working for Eli Lilly), when Eli Lilly drug company was sued that fluoxetine (Prozac) was allegedly causing suicide in some patients. That was well over 10 years ago. [I have no doubt that antidepressants save life (as for the group), but in some cases they may cause SI as the recent FDA warning draw attention to that effect. (This FDA warning happened after our patent application)]. So Tollefson and Eli Lilly in filing their patent would have had an increased duty to specifically give guidance and draw attention to any innovation on prevention of suicide or on the paradoxical effect of antidepressants (in addition that adequate guidance is a requirement anyway). They failed to do so. Tollefson and Eli Lilly would have had an increased duty to specifically give guidance and draw attention to our claims on the solution to preventing suicide and on solving the paradoxical effect of the antidepressants worsening depression, would they have felt that their method would teach or anticipate our claims and would be good and useful for these purposes. Tollefson and Eli Lilly would also have had the duty to inform the public, the professionals, the media, and regulatory agency (FDA) of any such conclusion, would they have made such a conclusion. They should have especially done that at the time the FDA director in his nationwide front page newspaper interview (and also under prime time media coverage) was teaching away from our methods. So far they did not do that, despite the very intense and unusual media (and professional) attention on antidepressants' risk of causing suicide, or any of the need of preventive measures thereof. Up to date there is still an unsolved long felt need for the solution that our application can be used for. Please also note the intense legal liability, would a drug company (Tollefson and Eli Lilly, or Chappell and Pfizer) hide such information (risk or solution) that the examiner alleges would be obvious from Tollefson's patent, or from the Chappell's publication. Such a huge legal liability (of not coming forward) had been exemplified by Merck drug company's liability and law suit(s) against them, as also depicted by the media. Merk's first patient lawsuit on Vioxx (causing the death of that patient) resulted in awarding to that single family $253 Million (even if the amount later was reduced). As per my recollection of other news on this topic Merk did not warn the public on the result of prior studies indicating the risk found, but went ahead and repeated the study instead hiding for years the problem [and solution of warning or of withdrawing their drug]). So not only that Tollefson and Eli Lilly (or Chappell and Pfizer) have not disclosed our claims and a solution for a long felt need, their silence is construed of teaching away (of that use).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.**

If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

As we have shown the prior arts cited does not anticipate our claims, but teach away.

The same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J).) "that references must ... suggest [our] claimed invention, or [the] examiner must present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." We have shown in this extensive reply why the thinking pattern of one skilled in the art would have been different from the examiner's reasoning, and why one skilled in the art could not have disregarded the boundaries of standard of care without adequate guidance, and without going through a risk/benefit/side effect, available alternatives analysis (etc).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 220 also states, that: "The prior art reference ... must teach or suggest all [our] claim limitations." **As we have shown (including the secondary factors) this is also not the case.**

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 222 teaches that in overcoming rejection based on obviousness, we can argue (and in this reply I think there is no doubt that we successfully did that) that "the combined teaching of the cited **references still fail to fully teach the invention recited herein**". At page 223 it sates: "**If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn**. (In re Rouffet, 149 F.3d 1350 (Fed. Cir.1998).)

Secondary factors also apply in regard of prevention of depression and depressive relapse. As secondary factor showing unobviousness of our invention, even more than four (or 4 ½) years after our application, others with major interests are still not teaching our method.

Examples for secondary factors:

1) **Previous failure of others** (See e.g. FDA directors' inability to give adequate solution – see inserts in reply to the 1st OA; suicide and antidepressant emergent suicidal ideation/suicide remains an unsolved problem)
2) **Solves insoluble problem** (See e.g. FDA directors' inability to give adequate solution; overcoming the strong teaching against with new risk/benefit/alternative analysis for the benefit of the group)
3) **The invention is in a crowded art** (There are a lot of inventions on antidepressants)
4) **Unsuggested modification** (e.g. for initial treatment substantially in everybody depressed; treatment of 1st choice; looking the interest of a group; lower dose of antipsychotics; etc)
5) **Unappreciated advantage** (for the paradoxical effect of antidepressant worsening depression; for the development of tolerance against the antidepressants; for antidepressants causing suicide; modifying course of illness, resisting SI ["prevention"] etc)
6) **Solution of long felt and unsolved need** (not solved by others) (e.g.resisting SI ["prevention"]); (See FDA director's inability to give adequate solution; see Tollefson / Eli Lilly and Chappell / Pfizer not recognizing the use for preventing the paradoxical effect of antidepressants worsening depression or causing suicide; and not speaking up in the midst of FDA and media attention.)

7) Contrary to prior art teaching (even in the light of intense media attention, and highly recognized experts like FDA chiefs; See Texas algorithm and others including NIMH sponsored studies) Contrarian invention,
8) Synergism (described in the application, and no prior art disclosed our description)
9) Prior art references would not operate in combination [inoperative combination] (low dose of antipsychotic is critical and essential – higher dose can cause the opposite, the treatment emergent unwanted effect [worsening of depression (depressogenic effect), treatment emergent anxiety, akathisia – linked to suicidality]; initial treatment for the interest of a group is essential;)
10) References teach away from combining (or its use) for non-TRD, non-bipolar depression [see Texas algorithm and others including NIMH sponsored studies]).
11) Therefore we have **unexpected results.**
12) Unrecognized problem at the time of our invention of the paradoxical effect of antidepressants causing suicide – at least by the majority of psychiatrists and the FDA.
13) Lack of implementation over 5 years later – even in the intense media attention.
14) New principle of operation - The invention is utilizes a new principle of operation. The applicant has blazed a trail, rather than followed one. (The reasons of using the antipsychotics, how even the "extended" non-DSM depressive symptom has an effect on other symptoms and the depression as a whole, and providing synergistic effect through each target point of these extended non-DSM, or depressive DSM symptoms, of how the psychological, medication and [gene expression] effects interact; of using the invention for the benefit of the group, new risk/benefit/alternative analysis – enabling and necessitating the use of the invention as a first choice of treatment and in substantially all (of said) patients, effect on cognitive distortion).
15) Inability of competitors - Competitors ("big pharma") could not claim and/or enable our new use invention despite of the long felt unsolved need, and even after more than five (or 6 ½) years later there is an inability – as exemplified e.g. by the FDA directors perplexing on the problem. In addition – as disclosed none of the prior art documents were in the possession of our invention.
16) Solved a different problem (than the cited prior art references – and we have enabled the solution to the problem).
17) No convincing reasoning The opposing European attorney (not the European patent office) has not presented a convincing line of reasoning as to why the claimed subject matter as a whole, including the differences over the prior art, would have been obvious.
18) Modifications necessary It would have been necessary to make modifications, not taught in the prior art, in order to combine the references in the manner suggested. (new risk/benefit/alternative analysis – for the benefit of the group – and comparing the current standard of care with new information presented (on BPD versus MDD), thus enabling and necessitating the use of the invention as a first choice of treatment in substantially all patients; low dose of antipsychotic is critical and essential – higher dose can cause the opposite, the treatment emergent unwanted effect [worsening of depression (depressogenic effect), treatment emergent anxiety, akathisia – linked to suicidality]; initial treatment for the interest of a group is essential; enablement through the reasons of using the antipsychotics, and how even the "extended" non-DSM depressive symptom has an effect on other symptoms and the depression as a whole, and providing synergistic effect through each target point of these extended non-DSM, or depressive DSM symptoms, of how the psychological, medication and [gene expression] effects interact; effect on cognitive

distortion; using the method for other new use (treating paradoxical effect of antidepressant worsening of depression and causing suicide, treating residual symptoms of depression, etc).
19) Claimed features lacking. Even if combined, the references would not meet the claims.
20) Multiplicity of steps required New steps are required to enable and use our invention (new risk/benefit/alternative analysis – for the benefit of the group; low dose; enablement [see above]; ; effect on cognitive distortion; recognizing problem of paradoxical effect of antidepressant worsening of depression to coming up with solution for resisting suicide).
21) Multiplicity of references. Even large number (3) of references would not render the invention obvious due to the new steps, modifications, new use, enablement and other reasons (e.g. Prior art references would not operate in combination [low dose]; as shown at page 73 "another line of reasoning" the authors of the cited prior art were not in the possession of our invention).

If the value of the secondary factors could be brushed off by a statement that others not using an invention [that is the invention of the prior art listed by the PTO and applied and interpreted as being obvious to our claims] does not mean patentability [for our claims] [of overcoming obviousness rejection], than these exact same secondary factors would not have been created by court(s) and by the (US) PTO guidelines, (since they would have no value). In fact, and in our case the opposite is true. Since a great number of secondary factors apply to our invention, together these support the novelty and un-obviousness. This is specifically true and is **intensified** in light of the intense media attention and potential legal liabilities of not coming forward and/or using the invention by the same companies that were cited against the applicant as "prior art". The artisans and **the authors of all of the cited prior art (patent) documents were not in the possession of our invention**. We described several other factors of why the authors of prior art were not in the possession of our method. Therefore all that, and the secondary factors together with our other arguments **clearly shows that the prior art is distinguishable** and the obviousness rejection should be withdrawn. Therefore at least substantially most of our claims should be allowed for issuance.

Introducing a new risk/benefit analysis which (along with other guidance) enables new methods to save lives at large scale is a surprising new discovery. The secondary factors also support to that fact.

The unsuccessful attempt by others to enable our method – and the necessitated discussion on a variety of prior art shows that this is a crowded art.

The example of the inventive steps leading to clozaril patent monopoly for over 37 years, and the similarities and dissimilarities with our application.

When I was in training at the Mayo Clinic, around 1992, I the atypical antipsychotic clozapine was just introduced for the treatment resistant schizophrenia (not depression!!!)
Since 1960's this drug was known to be antipsychotic, in the 1970's it was used in Europe but due to severe and potentially deadly side effect of agranulocytosis (low white blood cells fighting immunity) the drug was voluntarily withdrawn.
We asked the staff at Mayo that how come clazapine still enjoyed patent protection in 1990's without generic medication on the market. The staff psychiatrist said that reportedly the company claimed that they came up with new inventive steps allowing to be used (a) in a subpopulation of

patients (treatment resistant schizophrenia), (b) came up with weekly blood monitoring to catch a declining white blood cell count, (d) came up with a clozarpine registry to only dispense medication if the blood test was done and was within limits. We also asked that isn't it obvious, and the staff replied that as secondary factors showed it was not as nobody else came up with the same. In essence the inventive step was a new risk/benefit/side effect analysis. Indeed clozapine extended its' monopoly for 37 years after the discovery of this drug, US patent expiring in 1998.

> See also **US 3,539,573** and "Clozapine was developed by Sandoz in 1961. [see GB980853, and US3539573 not appearing until 1970; and GB1418363 and US3962248, - Other patents have focused on assessing the patients' suitability for such treatment – indicating that such an assessment and analysis similar to a risk benefit analysis as a step of our claims are patentable [WO9631621, WO9721833, WO9732037]- see also **Current Patents** 15 Nov 2002 week 0246 at http://scientific.thompson.com/media/cdjournals/gazettenews/202/CPG_News_0246.pfd]. (In the United States it was prescribed since 1989. [see also Stoner, S.C. et al A program to convert patients from Trade-name to generic clozapine Pharmacotherapy 2003; 23(6):806-810 [particularly page 806 second column 3rd line from the bottom on patent expiration. {For an article on the recent introduction of generic clozapine in Europe please refer to: Paton, C Generic clozapine:outcomes after switching formulations. British Journal of Psychiatry 2006. 189 184-185 /page 185 first column after the summary lines 4-7/].

The clozapine example also shows **marked differences** to our invention (**to our advantage**):

A) In case of clozapine the method (of administering the same medication was used even after the inventive step) as earlier clozapine was administered to the whole group of schizophrenic patients that have included (by definition and by chance) an unidentified subgroup of treatment-resistant schizophrenic patients as well. (The patentable discovery in case of clozapine was monopolizing on using a new risk/benefit analysis for that subgroup). In contrast, in our invention the aforementioned claim uses were never used before! This is a critical difference – an advantage - in allowing the issuing of our application.

B) It is also notable (what the clozapine patent owners could have used (and maybe did use) for argument and still winning) that there was a difference in in the risk/benefit analysis before and after the agranulocytosis and the lethal side effect became known. That is, earlier with the first introduction of clozapine psychotic patients could receive the drug simply because it was effective in treating schizophrenia. However, that old risk/benefit analysis was insufficient later once the agranulocytosis as serious side effect was revealed. Therefore the standard of care was changing and a new (third) risk/benefit analysis was required to overcome the obstacle (the skilled in the art's inability to use the drug). Once that was provided with patient monitoring (regular WBC/platelet count, new regulations on dispensing or no dispensing the drug) and by showing a long felt unsolved need, the method for a new invention was in place also leading to extending the patent life of clozapine for 37 years after it was known to have an antipsychotic action.

The point is that the risk/benefit analysis does change over time and "obviousness" for the skilled in the art was not in place to use clozapine once the agranulocytosis was known (at least not until the new risk/benefit analysis was explained).

That was an essential point that the clozapine patent owners could have argued if the PTO would have attempted "obviousness" objection for re-introducing clozapine and resulting in the patent extension of that drug through new patent applications.

Claims 140-144, reflects the similar inventive steps.

Showing difference between our application and of various other patents, patent applications and references:

(The unsuccessful attempt by others to enable our method – and the necessitated discussion on a variety of prior art shows that this is a crowded art.)

For all of the prior art references it should be noted, that none have overcome the strong teaching against of our method and no prior art even mentioned the need for a risk/benefit discussion of why to use our method as initial treatment. We on the other hand had substantial and detailed guidance of how to use our method, and went into the discussion of the benefit of the group, giving examples from other areas of medicine like how we were treating appendicitis relying on the same "benefit of the group" principle. (It was taught this in my European medical school as the benefit of the group coincides with the interest of the individual person since it is not known who in the group would be affected). We said that the prevention of suicide is the paramount factor.

We have also noted in the Utility page 2, 3, as regards of the strong teaching against of our method:

"There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)

A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987).

A book chapter reviewing this topic from year 2001 makes the point that "the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,).

This along with the analysis of the principles of how the patent monopoly for clozapine continued for about 37 years is also important in considering the patentability of our method. In the example of the clozapine patent monopoly new inventive steps were used allowing the reintroduction of the previously withdrawn drug from the market for a subgroup of patients where the new risk benefit analysis – along the guidance of the new inventive steps – did allow the use of this drug again. The patent monopoly for clozapine continued for about 37 years (in the USA). There are not only similarities, but to our advantage dissimilarities as well of this clozapine example that we have discussed above.

It is also notable and is known in prior art, that the severity of depression does not distinguish those who commit suicide from non-suicide attempters among patients with major depression (Beck et al 1985, as listed page 7 first column lines 4-7 in Mann JJ et al Evidence for the 5-HT hypothesis of suicide. British J Psychiatry 1989, 155 (suppl. 8) 7-14.)
Therefore there is a dissociation between depression and suicide and the two is not equal, and the reasoning for treating one is not equal for the reason of treating the other. We mention this to avoid any unconvincing lines of reasoning against our claims.

General discussion of how the cited prior art documents and some other relevant prior art **are different from our claims:**

Tollefson, US 5,958,921 Method for treating depression with olanzapine. (PCT pub WO97/23220) PCT filed December 04, 1996.
Based on the following evidence we feel that this Tollefson, (US 5,958,921) reference is misleading or was phrased in a deceptive manner as far as the suggestion for enablement for their broad claims. We could not find any enablement in the Tollefson reference for the purposes of our claims: Since over twelve (12) years of the filing of this application no corresponding publications in professional journals followed this Tollefson patent application regarding the use of olanzapine for non-psychotic, non-treatment resistant unipolar, or major depressive disorder, (or for the purposes of our other claims) it is highly doubtful that Tollefson was in the possession of surprising results or the conclusions drawn in our claims. Therefore this Tollefson, (US 5,958,921) reference and ours is clearly different. This is further exemplified below:

> As background information we would like to summarize the following: Claim 1, 9, and 12 and dependent claims of this Tollefson, (US 5,958,921) reference which claim a method for treating depressive signs, depression or Major depression not diagnosed with a psychotic condition, without referring that it would be a treatment resistant depression (TRD). They mention without details that the usefulness can be demonstrated by clinical trial, and also mention that such effectiveness was shown in an international double blind trial involving 1,996 subjects randomized 2:1 to either to olanzapine or haloperidol (5 to 20 mg per day) for six weeks, and olanzapine was significantly better then haloperidol wherein the haloperidol treatment group the worsening of depressive signs was demonstrated. (We will comment with our uncovering discovery on this trial below):
>
> Please compare this to Beasely, Tollefson at al Olanzapine versus Placebo and haloperidol. Acute phase results of the North American double-blind olanzapine trial Neuropsychopharmacology 14:111-123 1996

1) While the claims of Tollefson (US 5,958,921) make it clear that their intent was to claim treatment of patients "not diagnosed with a psychotic condition" (claims 1, 9, 12,) this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. Their alleged enablement – as disclosed by Tollefson – is restricted of demonstration by clinical trial (page 4 5th paragraph on my printout from the PTO web page). There is nothing mentioned if these patients were MDD with TRD, bipolar depression (within the category of depression) or at times patients with schizophrenia or schizoaffective disorder

showing depressive symptoms, (but right at the time of their assessment free of psychotic symptoms). If indeed Tollefson representing a major pharmaceutical company would have discovered a surprising new use (pre-requisite for an invention) for MDD, non-psychotic, non-TRD, – specifically with the number of patients referenced in his patent application being almost 2000, a publication in peer-reviewed clinical journals would have followed in over twelve years time. This applicant could not find anything of that nature. The corresponding publications were only for currently known use not conflicting with this applicant's claims. Therefore it is likely – and there is nothing to the contrary in Tollefson's patent application (the 5,958,921 reference), that the patients in the cited study of that patent application are a combination of MDD with TRD, schizophrenia (or schizoaffective disorder) with depression, and bipolar depression. The medical literature search corresponding to that patent application indeed reveals publications in these areas. It also has to be mentioned **as revealed in our application, that both bipolar disorder and TRD are associated with high percentage of psychosis** even if the psychosis often goes unrecognized. The language chosen by Tollefson of "a patient not diagnosed with psychotic condition" instead of using non-psychotic patient further reflects or supports that implication (i.e. that psychosis is not excluded, it is just not diagnosed). In summary, this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. [See also 3) below.] Specifically, and in addition, no enablement was provided for MDD non-TRD, non-psychotic patients, or for he purpose of our other claims.

2) It is also known that other Tollefson (Eli Lilly) reference (e.g.: **Tollefson, WO 99/61027, or US6,960,5577**) had study on MDD with TRD. We have also referenced in our application the Shelton study (2001 Am J Psychiatry) on TRD.

Now, it is a concern that the FDA has approved atypical antipsychotics – as monotherapy - for the treatment of bipolar disorder without specific warning that they may not be an equivalent alternative to the traditional mood stabilizers at least in subgroups of patients. It is known, that there is an overlap with psychosis in a high percentage of bipolar disorder patients:

> "**About 2/3rd of patients with *bipolar (manic-depressive)* disorder are having a history of at least one psychotic symptom**. Bipolar patients who are psychotic during one episode of affective illness are highly likely to be psychotic during subsequent episodes. [Tsai, SY. M., et al. 2002.])" (page 29 last four lines and page 30 1st line in our provisional application with size 14 copy).

Therefore, in bipolar disorder the antipsychotic monotherapy targeting psychosis, agitation, and anxiety may show a significant difference in the improvement of patients but only as for the group. That does not mean that the atypical antipsychotics can replace the traditional mood stabilizers for all subgroups (and in non-psychotic bipolar patients). Unfortunately the FDA and the clinical marketing did not draw attention to that potentially and likely misleading link. At least a subgroup of the bipolar patients who are withheld from the benefit of the traditional mood stabilizers may suffer, as the above fact/concerns were not mentioned or emphasized by the FDA. **The same may be true for the treatment of TRD**. As we noted in our provisional application (page 35 last 3 lines and page 36 lines 3-4):

> "It had been estimated that **a significant proportion, 15% of major depressive episodes fulfill the criteria for psychotic subtype**. (Gumnick, J.F. et al. 2000). ... ...Nierenberg had noted that **in many cases, the cause of treatment-resistant depression may be an unrecognized psychosis.** (Nierenberg. A. A., 1992)."

The Shelton study referenced in our application (2001 Am J Psychiatry) did show only a modest improvement with olanzapine monotherapy for the treatment of TRD, but as is known in a significant percentage of TRD the cause may be the unrecognized psychosis. That may

explain the overall difference, and also of why there was only for modest effect for the olanzapine monotherapy for TRD.
We provided enablement in non-TRD through various different mechanisms (as revealed in the reasons part) and also on the interaction of medications, psychological and [gene expression effect].
The Shelton, the Tolefson (5,958,921, **WO 99/61027, or US6,960,5577** references) **or similar studies on TRD therefore cannot be extrapolated without enablement to non-TRD. Therefore these references are clearly different from our claims.**

3) Tollefson also disclosed studies on the effect of olanzapine on "anxious and depressive symptoms accompanying schizophrenia". (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) In that study, Tollefson specifically stated that "anxiety and or depression may persist in the absence of overt psychosis" [in the schizophrenic patients]. (page 806 second column under discussion, line 5-7). Whether their patients disclosed in their study referred to in their 5,958,921 application as "not diagnosed with psychosis" included that patient population is unknown, thus the 5,958,921 reference was not presented in a clear and unambiguous way. If fact based on the presented evidence here we feel that it is misleading, as further evidenced next:
4) In the 5,958,921 reference Tollefson refers to their international double-blind study involving almost 2000 subjects randomized to receiving either olanzapine or haloperidol for 6 weeks. It is respectfully submitted that
   a) in order to conduct such a large scale study usually smaller non-double blind study is conducted and revealed. (We have not found such a study in the literature for MDD non-TRD, non-psychotic).
   b) It had been known in the literature (as it was also disclosed by the applicant) that haloperidol can cause depression. In fact Tollefson was also revealing that finding.
   c) With all that and with the knowledge of the art at the time of Tollefson's application it is respectfully submitted that no ethics (research) committee would have approved such a large scale study on unipolar depression or MDD with non-psychotic and non-TRD, and from the definition of unipolar depression on non-bipolar patients. They would not allow a known depressogenic agent the neuroleptic haloperidol (causing depression as revealed in the literature and also in our utility) to be used in the control group of one third of the 2000 patients, also because of the serious and potentially deadly side effects like tardive diskinesia (TD) and neuroleptic malignant syndrome (NMS). Also the neuroleptic haloperidol is known to cause akathisia (restlessness) that is linked of causing suicide. (see e.g. Drake R.E. Suicide attempts associated with akathisia. Am J. Psychiatry 142:4, pp 499-501, April 1985). **Therefore even tough the broad claims of the Tollefson reference covers unipolar depression or MDD with non-psychotic and non-TRD, it is quite convincing with absolute certainty that the patients in his study were not consisting of such - and based on the evidence we believe falsely claimed patients.**
   d) In addition claiming an antidepressant effect (for non-psychotic patients) in that Tollefson US 5,958,921 reference in comparison to a drug that is known to cause depression is a non-convincing rational. If you give a drug that is known to cause depression (haloperidol) and compare this with placebo and the placebo group would show a better mood that would not make the placebo an antidepressant.

e) As regards to patients with schizophrenia Tollefson has revealed that "the literature generally reflects that given an adequate dose and time interval for a positive symptom response to conventional antipsychotic drugs, some mood improvement will be seen". Pages 806 second column under discussion lines 18-21. (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) Therefore **no** generalization can be made of the "antidepressant" effect of antipsychotics for MDD non-TRD, non-psychotic patients.

5) In the 5,958,921 reference Tollefson makes mention of his intention of using the term "treating" including profilaxis, but no enablement for how that would be achieved, or proven by clinical trials were presented as far as the purposes of our claims.

In summary, the 5,958,921 Tollefson reference is not a clear and unambiguous disclosure or we feel based on the above it is even a misleading or deceptive, and no evidence was presented for enablement as regards to our invention. Therefore the two applications are clearly different.

Therefore, this document does not foresee our claims, (it is not enabling, has insufficient disclosure; it fails to put the subject matter of our claims within the possession of the public, that is someone with general skills in the field could have not used the referenced document with their own knowledge to make our claimed invention themselves; so it does not affect the novelty of our application.

Tollefson, WO 99/61027 Combination therapy for treatment refractory depression (priority date May 22 1998 PCT/US99/11276).

and

Tollefson, US6,960,5577, Combination therapy for the refractory depression.

These methods are concerning Treatment resistant depression only as per their enablement.
We have already made comments these WO 99/61027 and US6,960,5577 on referencing the other Tollefson US 5,958,921 above.

Tollefson makes a mention (e.g. WO 99/61027) under the section "clinical trials" using a language of "in one such study" and refers to a study done on treatment resistant depression (TRD), but in fact there is no evidence to the contrary and that conclusion is supported by that there is no publication in over ten (10) years in the literature involving non-TRD non-psychotic unipolar or major depressive disorders, the subject of our invention. As we mentioned above the two patient group is drastically different. Due to the overlap with psychosis revealed in the literature [see #2) under Tollefson, US 5,958,921 above].

In addition, Tollefson's (WO 99/61027) use of the medication combination for rapid onset of action would not anticipate our claim. The same author Tollefson have published that the time to respond to antidepressant fluoxetine [alone, not in combination] was noted at Week 1, which is within the same time frame that he is claiming in the patent application for "rapid onset of action". Therefore Tollefson cannot claim (and in the approved patent did not have any claim about that) that the combination use would be a rapid onset when he published that the monotherapy fluoxetine achieved about the same time frame for response. (Tollefson G.D. at al How long to onset of antidepressant action: a meta-analysis of patients treated with fluoxetine or placebo. International Clinical Psychopharmacology 1994, 9:245-250.).

Similarly, and in accordance with Tollefson's 1994 publication, research also showed that the rate of action of oral older tricyclic antidepressants were found to act early in the responders within the first week of treatment. (Katz M.M. The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychological Medicine 1987, 17:297-309. – copy is attached). So one could not expose the patients to the risk of antipsychotics if antidepressant monotherapy would show comparable or the same "rapid onset of action". Therefore no conclusions can be drawn of Tollefson reference anticipating our claims. That would be incorrect.

In addition, on page 13 Tollefson reference (WO 99/61027) gives "general outlines" and "some preferred dosages" for the antipsychotics, but they give an extremely wide range and not a low dose (or due to the wide range not specifically a low dose).
This shows no consistency for a low dose or preferred low dose, (or a concept that low dose would be preferred), as for olanzapine this range includes high dose (even when considering for the treatment of schizophrenia). In fact their preferred dose range for olanzapine –their own drug - includes a top range that is up to 33% higher than the FDA approved dose! For risperidone the preferred range is relatively still high and not a low dose. The low dose concept is crucial to avoid undue experimentation.
It had been known that olanzapine has treatment induced side effect that includes anxiety, agitation and akathisia. **(Beasely CM et al Olanzapine versus placebo and Haloperidol. Acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 14: 111-123 1996)**. In fact that paper specifically suggested some potential pharmacological contribution for more agitation, nervousness and anxiety with higher doses of olanzapine than with placebo. (page 121 second column lines 7-10.)

Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Document from **Tollefson and Eli Lilly company EP 0966967 A2.**
An opposing European attorney (not the patent office) also has submitted his observations to the European patent office regarding this reference.
This Tollefson EP 0966967 A2 is not enabling for non-treatment resistant non-psychotic unipolar or major depressive disorder patients, similarly to the above other Tollefson references.
The opposing European attorney's (not the patent office's) allegation leaves out the fact that - without the risk benefit alternative analysis and without explicit discussion of how this document would overcome the deviation from the standard of care and use that technique for non-psychotic, non-treatment resistant depression, - this document (EP 0966967 A2) cannot be enabling. The above document would not be enabling for deviating from the standard of care for our new use (and) as for initial treatment. As discussed above, that enabling is lacking and the clinical trials do not provide any evidence for non-treatment resistant cases, in fact it specifically mentions only a patient population with treatment resistance. Going into a theoretical case that even if they would have disclosed and discussed a research study involving non-treatment resistant patients they would still have to go through an analysis that we went trough that why the benefit of the group would substantiate to override the currently used and known risk benefit analysis. We have quoted from our provisional application:

> **"One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.**

> This speculation is probably correct, **but by itself would not substantiate the added risk using the neuroleptics.** With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, **it is the decrease of suicide rate that is the paramount important factor**. ..."

So they would have needed to go through a risk benefit analysis in this regard even if they would have had patients disclosed in their trial with non-treatment resistant depression. **None of those conditioned ifs were there** however in the Tollefson references.

We on the other hand did provide these steps and enablement. Deviating from the standard of care or not doing risk benefit alternative analysis is an automatic malpractice as it is also known in the risk management field within the medical art. The above mentioned document therefore could not anticipate our invention, and in fact there were inventive and additional steps involved.

Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Document from Tollefson and Eli Lilly company EP 0958824 A2

The opposing European attorney (not the patent office) misquotes the applicant: Document 2's (this) (page 2 [0001] describes their method for treating refractory depression or partial responders. The description of partial responder is less then 50% as was also stated by the opposing European attorney. However, the opposing European attorney errs with his following line of argument [page 7 (7.2) lines 6-7], as our claims did not encompass the non-response defined as less than 25%. (See also our utility page 10 lines 11-15; followed by lines 16-21 that the opposing European attorney disregarded):

"It is possible to have a response to an antidepressant treatment (i.e. better than a partial response or non-response), but still have residual symptoms, and not a full recovery. Therefore the combination may also be effective to treat residual symptoms of depression (which is a separate entity and not equal to partial response), to achieve full remission as a goal. In this case the risk/benefit analysis of giving a medication combination is also different from TRD." Thus that patient population is encompassing the patient population that document 2 (EP 0958824 A2) did not claim, the better than 50% (and not the less than 50%) responders. Additional step(s) a different risk benefit analysis was also revealed, along with the reasons of why we should give our method as an initial treatment.

Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Document from Nesbitt and Pharmacia & Upjohn company WO 02/053140 A2

The above document similarly to the Tollefson references (above documents) does not give any enablement of why to use the medication combination for the purpose of our claims.

It does also not give guidance for why and how the average artisan would be able to deviate from the current standard of care using that method (deviation from the standard of care without sufficient guidance/enablement benefiting the patient is defined as malpractice). There is no description or explanation of how the one skilled in the art could use the techniques of that document for the use of our claims, and contrary to the strong teaching against in the prior art.

There is no risk benefit alternative analysis in that document either. That document therefore is not enabling for the purpose of our claims, and as we have shown we did apply new steps for our new use so there is novelty and inventive step that we have applied.

Therefore this document is not enabling for the purposes of our claims and is different from our application.

Document from **Evins at al. (Am. J. Psychiatry 156:5, May 1999 pages 798-799.)**

The opposing European attorney (not the patent office) alleges that the above reference of using buproprion (an accepted anti smoking medication that happens to be an antidepressant) together with clozapine in schizophrenic patients (where the use of antipsychotic to target the hallucination and thought disorder is expected for that particular use) would make our method "obvious" even for non-psychotic patients. This logic is absurd and is not substantiated. Would the combination treatment for smoking cessation in non-psychotics be obvious that surprising result would have been commented on either by the authors or by the editorial staff.

This Evins publication is similar to George reference (**George** T.P et al A placebo controlled trial of buproprion for smoking cessation in schizophrenia. **Biol Psychiatry 2002; 52:53-61.**) that cannot be extrapolated from the treatment of smoking cessation in schizophrenia.
This data cannot be extrapolated to non-psychotic, as in psychosis the antipsychotics also help improving reality testing, the disorganized thought process and are targeting the response to hallucinations – all important aspects of the treatment of the psychotic individual, but not the depressed. One skilled in the art would realize, that with the use of antipsychotics, (and with a more effective treatment with atypicals), the symptoms of schizophrenia would improve, the patient with schizophrenia would be able to focus more to instructions, and follow counseling guidelines as part of most smoking cessation process. The relative difference or trend between atypical and typical antipsychotic drugs, in the better smoking cessation rates are not surprising as the newer (atypical) antipsychotic medications had been found to be generally more efficient in improving schizophrenia and psychosis, especially in subscales like (behavioral) withdrawal of the schizophrenics and negative symptoms. So with the overall improvement of the thought process of the schizophrenic individual, the smoking cessation rate can be expected to be better than those patients not getting treatment (or not as effective treatment) for their thought disorder. This would be understood by those skilled in the art. In accordance with this nothing is mentioned in George reference that the use of (atypical) antipsychotic with other antidepressants (or with buproprion, Wellbutrin, marketed for smoking cessation as Zyban) should be also tried in the light of this study in the non-psychotic, non-schizophrenic individuals. With such a surprising finding they would have made such a comment (or if they would have not, an editorial comment would have followed with such a suggestion). So, George's reference necessitates to amend of our claims (to be precise and exclude schizophrenia, and psychosis that is treated on a chronic basis with antipsychotics), but does not preclude the patentability of our invention in this regard. George's reference cannot anticipate our invention.

Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Theobald et al **US 2003/0049308 A1** (PCT filed Apr 2, 2001)

Transdermal or transmucosal dosage forms with a nicotine-containing active substance combination for smoker disintoxication.
The publication [0008] doees mention that the additional substance for side effects should be substantially ruled out. No further information on this is discussed.
The method is for transdermal or transmucosal application for treating nicotine dependency, but does not enable the method for why to use e.g. the neuroleptic.
At [0020] the publication tells that the active substance doses.. that are suitable for treating the psychological dependency are known to the skilled in the art, and no other explanation or reference is given.

The Theobald reference is not enabling for the purposes of our claims and are different from our application.

Document from **Ralph and Pfizer EP 1238676 A1**. (priority 01.03.2001)
The opposing European attorney (not the patent office) alleges that this prior art would take away the novelty for the purposes of at least some of our claims.
However, we are submitting that the prior art is not enabling for the purpose of our claims, therefore the alleged prior art rejection proposed by the opposing European attorney should be withdrawn.

The arguments are similar to the ones discussed under document from Tollefson and Eli Lilly company EP 0966967 A2; document from Tollefson and Eli Lilly company EP 0958824 A2; and document from Nesbitt and Pharmacia & Upjohn company WO 02/053140 A2.
The same applies as regards to the treatment of various substance abuses.
It should be also noted, that many of the abusable substances (e.g hallucinogens) can elicit hallucinations while other abusable substances like cocaine can elicit paranoia, in which the use of antipsychotic would be obvious. The substance abuse group is a heterogenous group and no general conclusions can be drawn based on the treatment of the above examples to the treatment of smoking cessation or withdrawal. If there is some rational not mentioned for these generalization that should be enabled and explicitly explained. The above reference in our understanding lacks such enablement and guidance
Document from Ralph and Pfizer is not enabling for that use of substance abuse (they only make a mere mentioning without reasons or explanations that would not allow the artisan to overcome the barriers and use it for the purposes of our claims). We on the other hand enabled our method through our description of the mechanism of action of the aforementioned class of medications on cognitive distortion and thus also for smoking cessation.
Even if (Ralph and Pfizer EP 1238676 A1) document would be enabled through one action (the substance abuse itself), that would not make another method acting on a different level (the cognitive distortion) unpatentable. (Just because gasoline is used to propel the engine of a car that does not mean that a hybrid car using electricity or hydrogen could not be patented).

Please note that the Beasely, Rasmusen and Tollefson US 6,159,963 Method for treating substance abuse (discussed below) and the (Battaglia J et al), a methodologically flawed but prior art to both Ralph and Pfizer EP 1238676 A1 and Beasely, Rasmusen and Tollefson US 6,159,963, is related and will be discussed below. (Battaglia J et al Structured assessment and depot fluphenazine treatment of multiple suicide attempters in the emergency department. International Clinical Psychopharmacology 1999, 14: 361-372.)

Hence we have shown that all of the allegations regarding prior art publications are only allegations from the (non-patent office) opposing European attorney.
Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Beasely, Rasmusen and **Tollefson US 6,159,963** Method for treating substance abuse. PCT filed March 10, 1997.
The reply is similar to what was said under Ralph and Pfizer EP 1238676 A1.
There is no enablement in this Beasely, Rasmusen and Tollefson US 6,159,963 document for their wide claims hallucinogens and opioids included, not nicotine, yet in claim 7 withdrawal from addictive substance (again nicotine is not specified) is claimed. Treatment of the cessation from nicotine is mentioned after the nonspecific mentioning of the trial but the phrasing of their sentence "a lower dosage may be more appropriate" and without explanation for that reason suggests that there were no such studies done, and definitely they do not enable the skilled in the art – aside of suggesting the use – for the use of the method for that purpose. (Please note our above discussion that that several of the above Tollefson references used a language that could mislead the reader). They only describe an experiment of auditory startle response in rat treated with opioids and mention a study of clinical trial suggesting that olanzapine can be useful for the treatment of addictive substances without any details whatsoever regarding of what substances from this broad group was tested. It would be crucial since many of the substances (hallucinogens) or their withdrawal (cocaine) can cause hallucination and paranoia where it would be obvious to use an antipsychotic. Other withdrawal from substances like nicotine in an ordinary smoker does not cause hallucination. Therefore without details, and without any publications following in the literature this (PCT/US97/03404) filed March 10 1997 application, this description was not enabling the skilled of the art to use this publication for the purposes of our claims.

Please note that the Ralph and Pfizer EP 1238676 A1 (discussed above) and the (Battaglia J et al), a methodologically flawed but prior art to both Ralph and Pfizer EP 1238676 A1 and Beasely, Rasmusen and Tollefson US 6,159,963, is related and will be discussed below. (Battaglia J et al Structured assessment and depot fluphenazine treatment of multiple suicide attempters in the emergency department. International Clinical Psychopharmacology 1999, 14: 361-372.)

Therefore these documents are not enabling for the purposes of our claims and are different from our application.

Battaglia J et al Structured assessment and depot fluphenazine treatment of multiple suicide attempters in the emergency department. **International Clinical Psychopharmacology 1999, 14: 361-372.**
This is a methodologically flawed but prior art to both Ralph and Pfizer EP 1238676 A1 and Beasely, Rasmusen and Tollefson US 6,159,963.
First, this publication pertains to treatment resistance and not initial treatment. Therefore for the reasons discussed under Tollefson, US 5,958,921 above specifically under #2) with the overlap of psychotic depression with TRD, the outcome of this article is not surprising, but does not say anything of the non-TRD group. However, there are other problems with the design of this publication, as it combines various diagnostic categories with an average of six (6) comorbid disorders of multiple suicide attempters; borderline personality disorder and alcohol dependence occurring most frequently, and reports the result as for the whole combined group. It is known that some antipsychotics are useful for the treatment of borderline personality disorders. (See page 34

with font size 14 in our provisional application and "Gabard's video 9/11/1992, – and published by APA 1995" on the use of antipsychotics in borderline personality disorder. – this precedes this Battaglia 1999 flawed methodology. [Alternatively see also Benedetti F et al Low dose clozapine in acute and continuation treatment of severe borderline personality disorder J Clin Psychiatry 1998; 59:103-107.]) Therefore no conclusions can be drawn from this article to our claims, because it is not known what diagnostic group was effected resulting in the positive outcome, and also because the patients were treatment resistant. In regard of the possible effect on alcoholism another preceding article to this publication (and of the above patent references of Ralph as well as of Beasely, Rasmusen and Tollefson) the Montgomery et al 1989 article (Montgomery et al Is there a relationship between serotonin receptor subtypes and selectivity of response in specific psychiatric illnesses? British J of Psychiatry 1989, 155 (suppl. 8) pp 63-70. page 66 first column 3rd paragraph lines 12-14.) mentions that 5-HT uptake inhibitors suggest a role in controlling the impulse to drink in bouts. In the same time antipsyhotics were known to usually be 5-HT2 antagonists as well as dopamine receptor antagonists. (Mann JJ et al Evidence for the 5-HT hypothesis of suicide: a review of postmortem studies. British J of Psychiatry 1989, 155 (suppl. 8) pp7-14, p 11 first column lines 11-12.)
However, in our view – as discussed further on below (under Pivac) there is a substantial difficulty on attempting enablement through neurotransmitter theories due to inconsistent results, and criticism toward the neurotransmitter theories. (See e.g. Steiner M. The neurochemistry of mood, Psychiat J. Univ Ottava, vol 14(2) 1989 pp342-343. p 342 first column lines 5-8.; Nair, NPV et al Neurochemical and receptor theories of depression. Psychiat J. Univ Ottava, vol 14(2) 1989 pp 328-341 p 328 first column lines 3-5 and 9-10.)
In possible further support of the controversy and difficulty with the neurotransmitter theory is that for 5-HT antagonists mianserin as well as antipsychotics like haloperidol is listed, and mianserin did not differ from placebo in preventing recurrent suicidal acts of borderline personality disorder patients not suffering from depression, while flupenthixol did. (Montgomery SA et al Br J. clin Parmac 1983, 15, 183S-188S, p 183S second column second paragraph, and p185S first column third paragraph. These are also referenced in Hirsch SR et al The concept and efficacy of the treatment of parasuicide. Br J. clin Parmac 1983, 15, 189S-194S table 1 on p. 189S.)

Of course, further problem that the skilled in the art should be aware but needed to be discussed is the akathisia related to the use of antipsychotics. (We did discuss akathisia in our utility within our guidance). So even though the above Montgomery study is on the treatment of repeated suicide of the borderline personality disorder, the use of depot flupenthixol neuroleptic would be concerning today due to the potential of akathisia that can lead to suicide. (For further interest please see also additional references on akathisia both from neuroleptics and from antidepressants as related to eliciting suicide: Van Putten T et al Behavoral toxicity of antipsychotic drugs, J Clin Psychiatry 48 [9, Suppl]:13-19, 1987, Drake RE et al Suicide attempts associated with akathisia Am J Psychiatry 142:4, April 1985; Shear, M.K. e al Suicide associated with akathisia and depot fluphenazine treatment. Journal of Clinical Psychopharmacology Vol. 3 (4) 1983 235-236. Blum A Patients at risk of developing severe side effects from depot fluphenazine treatment Am J Psychiatry 137:2 1980 254-255. Shaw ED et al A case of suicidal and homicidal ideation and akathisia in a double-blind neuroleptic crossover study J clin psychopharmacol Vol 6(3) 1986 196-197. Van Putten T. The many faces of akathisia Comprehensive psychiatry Vol 16 (1) 1975 43- 47. Zubenko G et al Antidepressant-related akathisia J Clin Psychopharmacol Vol 7(4) 1987 254-257. Lipinski J F. et al Fluoxetine-induced akathisia: Clinical and theoretical implications. J Clin Psychiatry 50:9 1989 339-342.)

Although we took a little detour in our explanation as the above cited references do relate to each other, but for conclusion:
The Battaglia J et al document are not enabling for the purposes of our claims and are different from our application.

Faour, US 20010048943,

Faour reference is a delivery patent not a new use patent. Although they describe "a method of treating depression, anxiety, and/or psychosis ... comprising administering **an osmotic device** which provides a controlled release of VFX [Venlafaxine, a selective serotonin and norenepherin reuptake inhibitor] from its core and a rapid release of an anti-psychotic agent", but from their description it becomes evident that this delivery system was intended for the use known in the art: Under 0004 line 2-6 they state: "On occasion, a person suffering from depression or anxiety and psychosis will be prescribed an antidepressant agent and an anti-psychotic agent. Rather than administering of two different dosages, it would be useful in the art to have available a single dosage containing both an antidepressant and an antipsychotic." They do not disclose nor do they give guidance anywhere in their application that the use of their delivery system would be for depression (Major Depressive Disorder) without psychosis, or without TRD. No risk/benefit alternative analysis or any guidance is given of why anybody should deviate from the standard of care, or even that one should think of a new use in this regard. In fact they list depressive states with (prevalent) psychosis (under 0091) and psychotic disorders with depression under 0093. One skilled in the art [without specific guidance in the patent] would have used this generic term of depression to apply the patent of Faour, over what was already known in prior art, that is to use the combination (and delivery systems) like for the treatment of psychotic depression, depression in schizophrenia and psychosis, in manic-depressive (bipolar) disorder (with or without psychosis, in depression seen in Borderline Personality Disorder (BPD), or for TRD. The skilled in the art could not have used their method for something that was not adequately disclosed, or for which no guidance was given of any sort.
This prior art reference does not give indication of initial treatment or to use their method as initial treatment on most everybody, changing the standard of care (and using risk/benefit alternatives analysis. Nor do this reference give indication for the prevention of suicide, prevention of the progression of the disease, treatment or prevention for the paradoxical effect of antidepressants worsening depression, or causing suicidal ideation, or for cognitive distortion, or smoking cessation (new use). In fact **in Faour, no disclosure is given of why the combination use would be of benefit** (for other than what was already known in the art).
The **Faour** reference cannot anticipate our claims.

Chappell, US 2002/0094986

The Chappell reference cannot render our invention obvious as Chappell is suggesting a combination of dopamine D4 antagonist in combination with an antidepressant for the purposes of their claims. However, in view of Kramer (**Kramer MS et al The effects of selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia Arch Gen Psychiatry 1997; 54:567-572**) the D4 antagonism does not prove antipsychotic activity as the selective D4 dopamine receptor antagonist in that study was ineffective as an antipsychotic.

Since the Chappell reference is specifically basing the argument of their combination on D4 dopamine receptor antagonist activity, and it failed to show that the aforementioned antipsychotic activity of any and all of the antipsychotic compounds in our invention is effected not by the D2 antagonism but specifically through the D4 dopamine receptor antagonist activity. This reference

also failed to show that such a D4 dopamine receptor antagonist activity would be statistically significant in percentage and in clinical effect to produce the needed antipsychotic effect and be clinically significant. Moreover, as we have mentioned in our specification (and provisional) that studies in depression have a particularly high placebo effect up to about 70 percent, the reference has also failed to show that the aforementioned D4 dopamine receptor antagonist activity would be sufficient (in their effect, through that action, in their percentage of their antipsychotic action – if there would be any from that receptor activity) to still provide a clinically significant effect despite of the high placebo effect. (Designing such studies would be possible for example with method similar to the Kapur reference provided in our provisional application).
Therefore no convincing line of reasoning was shown for the Chappell reference rendering our invention obvious.
Chappell's abandoned publication gives the impression that they use the term depression as a wide range definition that specifically include psychosis (under page 1; 0009 line 8-9) schizoaffective disorder depressed type. On the other hand nowhere in their specification they mention that Major Depressive Disorder without psychosis or without TRD should be also included in their method. This wide range definition is troublesome (just like an even wider definition like "psychiatric illnesses" or illnesses would be), without them giving disclosure, a guidance or reason. Under 0020 lines 7-10, they further give indication that their method may be used for TRD: "it is possible to treat depression... in patients for whom conventional antidepressant ... therapy might not be wholly successful".
One skilled in the art [without specific guidance in this abandoned publication] would have used this generic term of depression to apply the publication of Chappell, over what was already known in prior art. **The skilled in the art could not have used their method for something that was not adequately disclosed, or for which no guidance was given of any sort.**
This prior art reference does not give indication of initial treatment or to use their method as initial treatment on most everybody, changing the standard of care (and using risk/benefit alternatives analysis. Nor does this reference give indication or adequate disclosure for the prevention of suicide, prevention of the progression of the disease, treatment or prevention for the paradoxical effect of antidepressants worsening depression, or causing suicidal ideation, or for cognitive distortion, or smoking cessation (new use). In fact **in Chappell, no disclosure is given of why the combination use would be of benefit.**
The **Chappell** reference cannot anticipate our claims.

The Chappell reference was not enabling to the purposes of our claims, therefore cannot be applied against our invention as prior art with insufficient disclosures.

Pivac Collegium Internationale Neuro-Psychopharmacologium (C.I.N.P.) XXIIIrd Congress Montreal, Canada, 23-27 June 2002. Psychiatria Danubia 2002; Vol 14, No 3-4, pp231-242. – and any similar reference mentioned herein:

A) "Pivac et al. discloses that atypical antipsychotics ... should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph)."
Even if Pivac would have not just merely mentioning a synergestic effect without enabling it, that reference would still not anticipate or make our invention obvious:
It had been conceptualized [as also referenced in the above Ferris reference (Ferris R.M. et al Buproprion: A new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic β-adrenergic, serotoninergic (5-HT-2), α2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 1983 22, No 11 pp 1257-

1267. (page 1257 summary lines 13-14)] that down-regulation of CNS receptors had been commonly implicated in the mechanism of action of antidepressant drugs. **Kuoppamaki M. at al (Differential regulation of rat 5-HT2A and 5-HT2C receptors after chronic treatment with clozapine, chlorpromazine and three putative atypical antipsychotic drugs Neuropsychopharmacology 13:139-150, 1995)** showed that while risperidone had affinity to 5-HT2A receptors, chronic treatment with risperidone had no significant effect on 5-HT2A receptor binding (see page 144 last two lines of second column). Kuoppamaki had concluded that "**it may be that also other properties** ... than high 5-HT2A receptor occupancy **are needed** to elicit down-regulation of 5-HT2A receptors (p 147 first column lines 32-36.). Thus Pivac's simple statement that atypical antipsychotics have affinity to the 5-HT2A receptors would not explain in light of Ferris and Kuoppamaki of explaining of how antipsychotics would augment the effects of SSRIs or of how the theory of down-regulation of CNS receptors that had been commonly implicated in the mechanism of action of antidepressant drugs would fit in with these results. Therefore the argument that the Pivac reference would be rendering our invention obvious is not convincing.

B-1) As we mentioned under Battaglia J et al document the antipsyhotics were known to usually be 5-HT2 antagonists as well as dopamine receptor antagonists. (Mann JJ et al Evidence for the 5-HT hypothesis of suicide: a review of postmortem studies. British J of Psychiatry 1989, 155 (suppl. 8) pp7-14, p 11 first column lines 11-12.) In fact that was known with reference for over 25 years ago (see in Coccaro EF Central serotonin and impulsive aggression. Br Jounal of Psychiatry 1989, 15 (suppl 8), 52-62, p 59 first column lines 10-12 with reference to year 1984). Many of the above mentioned patents had been approved with the existence of this information not making their conclusions obvious either.
However, in the focus of this paragraph B) there is a substantial difficulty on attempting enablement through neurotransmitter theories due to inconsistent results, and criticism toward the neurotransmitter theories. (See e.g. Steiner M. The neurochemistry of mood, Psychiat J. Univ Ottava, vol 14(2) 1989 pp342-343. p 342 first column lines 5-8.; Nair, NPV et al Neurochemical and receptor theories of depression. Psychiat J. Univ Ottava, vol 14(2) 1989 pp 328- 341 p 328 first column lines 3-5 and 9-10.)

There had been references (see summary in Reeves' 2008 article (Reeves H et al, Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychiatry 69:8 2008 1228-1236. page 1229 first column 9-10) that suicidal patients have high hydroxyindolacetic acid in the CSF, but Mann (1998, at page 8 lines 3-4) mentions that some but not all studies have reported lower 5-HIAA and/or 5-HT in brain-stem regions of suicide victims. (Mann JJ et al Evidence for the 5-HT hypothesis of suicide a review of postmortem studies. British J of Psychiatry 1989 155, (suppl 8) 7-14.)

Also contrary the one sided mentioning of the Reeves' above 2008 article (page 1229 first column 16-19) - the postmortem studies on serotonin receptors in suicide are not equivocal, 4 out of eight studies have find greater binding (increase) for 5-HT2 postsynaptic receptors (p 53 last paragraph of first column in the 1989 Coccaro article). In addition the postmortem studies involve a heterogenous diagnostic group. (Coccaro E F. Central Serotonin and impulsive aggression. British J of Psychiatry 1989 155, (suppl 8) 52-62.
The same Coccaro article lists on page 58 second column line fifth from the bottom that neuroleptics have 5-HT2 binding affinity, and that reference precedes **26 years** Reeves' above

randomized, double-blind, placebo-controlled study so it cannot possibly be brought up for obviousness for using the aforementioned medication combination for the reduction of suicidality in MDD. Otherwise the whole industry including the psychiatrists, pharmacologists, the drug companies, the FDA and recently FDA chiefs perplexing on the lack of solution in prime time media attention – as presented under the secondary factors – and the media for not speaking up with the solution would all be liable for the death of millions worldwide over the years. That would be very odd specifically that there is only now a financial incentive from the drug companies to come up with new indication(s) of their expiring patent drug and with that getting patent extension from the FDA (in the US).
Similarly, in the 1989 Mann article, (page 11, lines 11-17) it is mentioned that antipsychotics are usually 5-HT2 antagonists, but in treatment implications in the next page they are not making any recommendation for their use. (Mann JJ et al Evidence for the 5-HT hypothesis of suicide a review of postmortem studies. British J of Psychiatry 1989 155, (suppl 8) 7-14.) Please note the cited knowledge was preceding **20 years** the Reeves' above randomized, double-blind, placebo-controlled 2008 article.
Meltzer (1989) (page 28 first column third paragraph) mentions that higher number of 5-HT2 receptors were find in depressed patients that normalized after antidepressant therapy. (Meltzer H. Serotoninergic dysfunction in depression. British J of Psychiatry 1989 155, (suppl 8) 25-31.) suggesting a solution with the antidepressant treatment alone.

Reeves' above 2008 article (page 1229 first column 7-9) brings up that suicidal behavior suggests dysfunction of dopamine neurotransmission without further reference to dopamine metabolism, or to antipsychotic drugs. In contrast and showing contradiction, Nair NPV et al reports that the functional dopamine activity may be reduced in depression. (Nair NPV et al Neurochemical and receptor theories of depression Psychiatr J. Univ Ottava Vol 14 (2) 1989 328-341, page 330 first column second paragraph). In Reeves' 2008 reference it is not explained of how further blocking the reduced dopamine activity with antipsychotics would be helpful - showing a one sided approach. In fact stimulants increasing dopamine are used in the depressed. We have discussed some of these contradictions in our application.
Karoum F et al reports lover concentration of HVA level (DA metabolite) in depressed patients who had attempted suicide, and also note (in discussing schizophrenia) that treatment with neuroleptic agents (antipsychotics) decrease levels of plasma HVA, thus showing again contradiction, and not allowing of drawing premature obviousness to our claims based on the neurotransmitter theory. (Karoum F et al Marked reduction in indexes of dopamine metabolism among patients with depression who attempts suicide. Arch Gen Psychiatry 49, 1992 447-450. page 447 last two lines of first column and first two of second one, and p448 last four lines of second column.)

So there is a problem with enabling a method strictly by neurotransmitter theories, and attempting to draw false conclusions for obviousness.

B-2) In possible further support of the controversy and difficulty with the neurotransmitter theory is the data that for 5-HT antagonists both mianserin as well as antipsychotics like haloperidol is listed, and mianserin did not differ from placebo in preventing recurrent suicidal acts of borderline personality disorder patients <u>not</u> suffering from depression, while flupenthixol did. (Montgomery SA et al Br J. clin Parmac 1983, 15, 183S-188S, p 183S second column second paragraph, and p185S first column third paragraph. These are also referenced in Hirsch SR et al The concept and efficacy of the treatment of parasuicide. Br J. clin Parmac 1983, 15,

189S-194S table 1 on p. 189S.) Please also see **G)** for mianserin being a potent 5-HT2 antagonists (Montgomery S. et al Is there a relationship between serotonin receptor subtypes and selectivity of response in specific psychiatric illnesses? Br Journal of Pyschiatry 1989 155 (suppl. 8) p 63-70, page 67 second paragraph.).

C) Confounding the theory in regards to the role of 5-HT2A receptors, and making any conclusions difficult on the agents acting on 5-HT2A receptors is the sharp contrast of in vitro and in vivo studies on the 5-HT2A receptor mRNA levels. While **Toth M et al (Antagonist-mediated down-regulation of 5-hydroxytryptamine type 2 receptor gene expression: modulation of transcription Molecular Pharmacology 45:11095-1100, 1994)** have demonstrated in vitro that mianserin has down-regulated the 5-HT2A receptor mRNA (page 1098 second column second paragraph's first two lines), an in vivo study by **Roth BL et al (chronic mianserin treatment decreses 5-HT2 receptor binding without altering 5-HT2 receptor mRNA levels European Journal of Pharmacology – Molecular Pharmacology Section, 207 (1991) 169-172)** had shown that mianserin did not alter the receptor mRNA level (p 171 second column last paragraph). Therefore the argument that the Pivac reference would be rendering our invention obvious is again not convincing.

D) At the Pivac reference the synergestic effect of M100907 and fluoxetine is explained "because of 5-HT(1A) autoreceptor blocade" (page 236 of Pivac first column "a new combination" line 4-7). At the same page of this article (p 236 second column line 7-9) they explain that pindolol as 5-HT 1A antagonist can also potentiate the effects of SSRIs. Now that raises grounds for opposition both clinically, and from patent prosecution standpoint in various ways.

D/a) Prior art reference (Cremers) showed that pindolol's blockade of presynaptic 5-HT(1A) autoreceptors does **not** augment the SSRI-induced 5-HT increase in the guinea pig brain. "Therefore very unlikely that the favorable effects of combining pindolol with SSRIs, as reportefirst second paragraph lines 1-3) **(Cremers TI, et al Is the beneficial antidepressant effect of coadministration of pindolol really due to somatodendritic autoreceptor antagonism? Biol Psychiatry 2001 Jul 1; 50(1):13-21.).** Therefore, there is no evidence shown in prior art that the atypical antipsychotics, would show more or less blockade of the presynaptic 5-HT(1A) autoreceptors than pindolol which did not augment the SSRI-induced 5-HT increase and was found to be very unlikely that the favorable effects of combining pindolol with SSRIs would be indeed due to 5-HT(1A) antagonism. In particular, the PTO (or anybody claiming obviousness) has failed to show that to each and every atypical antipsychotic medications. Therefore such a line of reasoning would not be convincing and the rejection for obviousness should be withdrawn.

D/ b) Moreover, another, the Jordan reference (WO 02/060423) at page 2 lines 22-24 specifically refers to the compound in that invention (see page 15 circled by the PTO as aripriprazole) was allegedly was "enabled" of having agonistic activity (not blockade) on the 5-HT1A receptor subtype compared to their reference compound. [At page 4 lines 8-9 they also reference buspirone having also 5HT1A receptor agonist activity of which we will refer to later]. Therefore, in any of these articles there is no prior art evidence to show if the atypical antipsychotics would show more or less blockade of the presynaptic 5-HT(1A) autoreceptors than pindolol, and therefore in view of **Cremers** (above) if they would or would not explain favorable effects of combining these substances with SSRIs; and that effect would indeed be

due to 5-HT(1A) antagonism. Also, in view of Cremers, it is also not clear that what degree of 5-HT(1A) antagonism would be necessary for a drug to sufficiently augment the SSRI induced 5-HT increase (since the effect of pindolol was unlikely carried out through such an explanation).

D/ c) In addition, as we have discussed in the **Pivac reference the synergestic effect of M100907 and fluoxetine is explained "because of** 5-HT(1A) autoreceptor blocade" (page 236 of Pivac first column "a new combination" line 4-7). At the same page of this article (p 236 second column line 7-9) they explain that pindolol as 5-HT 1A antagonist can also potentiate the effects of SSRIs. (p 236 second column line 7-9) they explain that pindolol through the same 5-HT 1A antagonist mechanism. However, it was shown that augmentation of antidepressant effect (for treatment resistant depression) by pindolol was no more effective than placebo. **(Perez V et al A double-bind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry. 1999; 56(4):375-379.**). Therefore, in view of **Perez and Pivac** that attempt through such molecular explanation and similarity with pindolol would not be enabling and would not make our invention obvious.

E) Another ground for opposition against obviousness is clinical. **Even if** there would be a sufficient answer to all of the above; the clinical risk benefit analysis a new and inventive step to apply our invention as initial treatment; for the claimed purposes and for substantially all or all patients (within the claimed group) would be still not proven/enabled in the prior art.

F) In addition if another non-antipsychotic agent, either pindolol or one like pindolol would have a similar receptor profile (i.e. both to pindolol and to the atypical antipsychotics – as that similarity on 5-HT1A receptor is claimed by the Pivac reference), and if indeed these agents would have the same efficacy, than that non-antipsychotic agent with less side effect (no NMS no TD) would be considered first to the antipsychotics according to the risk/benefit alternatives at the time of our invention and according to the same receptor profile as claimed by Pivac. Therefore it would not be obvious to use the antipsychotic over pindolol. The risk/benefit/side effect analysis cannot be left out.
(We on the other hand also gave guidance in our utility that the combination of an antidepressant with an antipsychotic is likely be superior to another augmentation strategies like two antidepressants. (See page 14 lines 9-12). [However, the non-antipsychotic agent simply based on the 5-HT1A receptor profile would not decrease cognitive distortion or likely would not be as effective in decreasing SI. See alsoB-2] above].

G) In addition there are other 5-HT2 antagonists aside of the antipsychotics. If they are considered safer, the risk benefit analysis would not allow for the use of the antipsychotics unless sufficient guidance is given of why that would be preferable. The above prior art references like Pivac lacked such a disclosure.
Mirtazapine an antidepressant is an antagonist of 5-HT2A (Poyurovsky M et al Mirtazapine for the neuroleptic-induced akathisia. Am J psychiatry 158:5 2001 p819 second paragraph first sentence.)
Other drugs that are effective in treating migraine are also potent 5-HT2 antagonists, ergotamine, dihydroergotamine, methylsergide and pizotifen, as well as the antidepressant amitriptiline and mianserin. (Montgomery S. et al Is there a relationship between serotonin receptor subtypes and selectivity of response in specific psychiatric illnesses? Br Journal of Pyschiatry 1989 155

(suppl. 8) p 63-70, page 67 second paragraph.) Please note that experiment under B-2 with mianserin would contradict to this theory that this mechanism of action would be responsible for the desired effect decreasing suicide (even though this was treatment resistant group and for a different diagnostic group of borderline personality disorder).

[As we have shown above the speculation on the blockade of presynaptic 5-HT(1A) autoreceptors (see **Cremers**) does not stands firm, and would not make our invention obvious. The apparent lack of enablement in the cited reference(s) (Pivac) or unconfirmed speculation based on the blockade of presynaptic 5-HT(1A) autoreceptors does not stands firm (**Cremers**). However, that would not jeopardize the enablement of our invention, as we enabled our compound and the medication combination through a different mechanism(s). This is specifically true for the effect on cognitive distortion and for the decrease of suicide rates.]

H) Among other medications or strategies that would be considered safer for increasing serotonin activity would be the above mentioned antidepressant adjunct therapy (to the first antidepressant), or increasing the serotonin activity with lithium as lithium is also know to enhance serotoninergic activity. (Meltzer H Serotonin dysfunction in depression. British J of psychiatry 1989 155 (suppl. 8.) 25-31. page 28 second column first paragraph.)

Jordan, (Otsuka pharmaceutical) **WO 02/060423 A2**

In addition, since an interaction occurs between 5-HT1 and 5-HT2 receptors at the individual neuronal level, all what we have under Pivac also stands here.

At page 2 (lines 22-24) the Jordan reference states that it has not been reported before that compounds in the present invention / aripprazole, have agonistic activity at 5-HT1A receptor subtype. Their alleged "enablement" is restricted to showing that activity of their test compound with a reference compound. (page 18). At page 4 they refer to a WO reference disclosing "5HT1A receptor agonist, buspirone". The Jordan reference does not enables aripriprazole in clinical trials (or in any other ways) of being efficacious for the treatment of depression that they claim (e.g their claim 2, 21, 22; [and in claims 19, 21 drug addiction]. Jordan specifically does not enable aripriprazole for initial treatment or for our other claims. The sole enablement is based on, having agonistic activity at 5-HT1A receptor subtype **just like** the compound **buspirone** that was cited by them:

It is therefore notable that buspirone is not approved by the FDA for the treatment of depression. In fact buspirone is also **not** used off label for the treatment of depression. While some open studies initially suggested efficacy for buspirone for an augmentation strategy with SSRIs a controlled study available at the time of our invention did not support that use, yielded negative result, and was not more efficacious than placebo. (**see enclosure. M. Landen et al A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J. Clin Psychiatry 1998; 59:664-668.**)
At minimum, in view of Landen, the uncertainty on the effectiveness of buspirone to augment treatment resistant depression needs to be acknowledged.

Therefore in view of the above, at the time of our invention the average skilled in the art based on the Jordan publication could not anticipate our invention. The sole alleged "enablement" of Jordan is based on, having agonistic activity at 5-HT1A receptor subtype just like the compound buspirone. Buspirone is not approved by the FDA for the treatment of depression.

The Jordan reference specifically does not enable initial treatment or the other usage of our claims.

Even if we further analyze the Jordan reference we cannot find enablement.
In the Jordan reference aripriprazole was being described as having agonistic activity at 5-HT1A receptor subtype (page 2), while buspirone being 5-HT1A receptor agonist (page 4 line 8-9) and buspirone being 5-HT1A partial agonist (page 4 lines18-19).
The Jordan reference (page 4) makes a reference that another agent gepirone (being 5-HT1A partial agonist) (page 4 lines 25-), **not** quite sharing the same receptor profile as aripriprazole. Note that their test compound was described as having agonistic activity at 5-HT1A receptor (and at page 22 demonstrating high affinity binding to H5-HT1A receptors). They note that another agent gepirone (being 5-HT1A partial agonist) can be combined with an antidepressant to effectively treat depression. That was in the context that this two compound not quite sharing receptor profiles. (Jordan reference (page 4) as above).

However, even if the disclosed gepirone and aripriprazole would share the same receptor profile, the following fact was known in the art that two serotoninergic antidepressants can be combined to treat treatment resistant depression. That however does not make our claims obvious. The enablement of the Jordan reference is done simply by having agonistic activity at 5-HT1A receptor, however that does not give enablement to our claims.

In our specification / or response we described if safer (non-antipsychotic 5-HT would be available that should be used over an antipsychotic secondary to risk/benefit/side effect analysis profile. We specifically highlighted the antipsychotic's role (e. g. overlap with cognitive distortion and effect on depression thought cognitive distortion, that buspirone or gepirone would not effect. Therefore the 2 compounds are not replaceable simply on basis of 5-HT(1A) activity, or for our reasons (effectiveness) to "prevent" SI.

Furthermore, as it was shown even if sharing exactly a receptor profile like being a serotonin receptor reuptake inhibitor (SSRI) there is no guarantee for clinical effectiveness as there were many SSRI's under clinical trial that were not better then placebo and were withdrawn from clinical research. In addition even several years later (over six and a half from our provisional application), the only published studies on aripriprazole are for adjunct treatment for treatment resistant depression (TRD) (now FDA approved for that indication). However as we said before that is not surprising based on prior art that shows overlap between psychosis and TRD. (see Tollefson, US 5,958,921 under #2) second bolded part on TRD.)

Therefore the Jordan reference does not anticipate or enable or our other claims.

Furthermore, what is further clouding the issue to make conclusions from the receptor binding or affinity level (as the only source of "enabling" and information for the Jordan reference) on the clinical effect of a drug is that it was described that in contrast to the classical theory that described that certain cells possess only a single neurotransmitter transmission (or receptor) was found to be incorrect. In addition, according to the so called "agonist directed trafficking", single receptors interacting with multiple pathways may result in that the pattern of intracellular signaling may differ depending on the agonist. So simply from a receptor binding or affinity the cited references and examples also attest to that confusion) the one cannot assume anticipation that a clinician (skilled in the art) with that knowledge would go ahead with these uncertainties and give these (experimental) drugs to a patient without sound clinical reason and without undue experimentation. It is of note that

aripriprazole was not FDA approved at the time of our priority date, at the time of the submission of our provisional application to the best of my recollection. In short anticipation and obviousness could not occur from the Jordan (or Pivac) references as the above sections also point that out.

Hirose S et al. An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. J. Clin Psychiatry Vol 63, (8) August 2002, pages 733-736.

It is respectfully submitted that this is not a prior art, it followed our priority date. Therefore we request the objection to be withdrawn.

In addition this document is not addressing many of our claims.

However, the following two notes should be also noted:

1) There is a substantial methodological error in this publication regarding the conclusions that they want to draw from the study. They conclude that combination of risperidone and fluvoxamine (an SSRI) from the beginning of the antidepressant treatment enhances the therapeutic response rate in depression.
This article is discussing treatment as initial treatment for non-psychotic patients, and the publication is **not** going into the expected analysis of separating the responders from the non-responders, and it's result statistically likely to reflect exactly only that difference. Hirose is not going into any risk benefit alternative analysis that would necessitate the use of his method for initial treatment.
We on the other hand have stated in our extensive provisional application (as discussed above under Tollefson) that:

> "**One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.**
>
> This speculation is probably correct, **but by itself would not substantiate the added risk using the neuroleptics.** With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, **it is the decrease of suicide rate that is the paramount important factor.** ..."

Even if, we would have filed late (but we did not), the opposing European attorney's allegations would still not prevent us from patentability due to our disclosure and new inventive steps as regards to the benefit of the group and other steps mentioned above.

2) Following right after the Hirose article is Barbee J G et al's article Lamotrigine as an augmentation agent in treatment-resistant depression. J.Clin Psychiatry 63:8 August 2002 p 737-741. Taken into consideration of the methodological flaw of the Hirose article, this publication may suggest the clinician reading both articles that an anticonvulsant medication in devoid of side effect like TD and NMS may be also tried as initial treatment (with the same flawed logic) enhancing the therapeutic response rate in depression since the responders and non-responders (TRD) group is not separated. Other considerations for the well skilled in the art may also apply.

The fact remains that the Hirose publication is not a prior art and followed our priority date.

Tsai et al. US 6,228,875 Methods for treating neuropsychiatric disorders. (Filed April 14, 1999)

It is notable that it was known prior to this Tsai reference that NMDA receptor antagonists like ketamine have hallucinogenic (side) effect and that had been used for a model for psychosis. The Tsai et al US 6,228,875 reference discusses the combination of

Partial agonist of the glycine site on NMDA receptor (such as D-cycloserine
Or a full agonist (e.g. D-serine or D-alanine)
Or a glycine reuptake inhibitor (e.g. N-methilglycine)

Their method entails a composition that contains an agonist of the glycine site, or a glycine reuptake inhibitor.

Claim 1, or 4 claims a pharmaceutical composition comprising of at least one agonist of the glycine site or a glycyne uptake inhibitor [increasing glycine level] and a second agent from the group including of antidepressants and antipsychotics wherein for claim 1 they are introducing some limitations. It is to be noted that in our provisional application we have referenced a publication (that was predating the Tsai filing date) that DCS (Seromycine) with a partial agonist character at the GLY site and with an NMDA antagonist-like effect (or mixed agonist/antagonist effect) had been shown to display prompt antidepressant effects. It was also known in the art that two antidepressant and for certain reasons like psychotic depression an antidepressant and an antipsychotic can be combined.

Claims 7 and 11 claim an agonist of the glycine site for the treatment of depression, and claim 33 combines this with second agent including an antidepressant and an antipsychotic.

Under examples they disclose a study on patients having schizophrenia. No other enablement is provided, specifically none for the purposes of our claims.

The Tsai document cannot foresee our claims (e.g., antipsychotic-antidepressant combination for treatment of a patient suffering form major depressive disorder [MDD](non-psychotic, non-treatment resistant); or for a patient having cognitive distortions with functional impairments; to give our combination for the prevention of suicide for patients suffering from [MDD](non-psychotic, non-treatment resistant), to give our combination as an initial treatment; or to giving our combination for protecting or remedying the development of tolerance toward the antidepressant, to avoid the paradoxical effect of an antidepressant to sensitize patients to depression; to give our combination for smoking cessation or nicotine withdrawal).

In addition most recently almost ten years following the filing of his application Tsai published in a psychiatric newspaper in the December 2008 disclosing that "Thus far, NMDA-enhancing agents have been tested mainly as add-on treatment for patients on stable antipsychotic regiments." A study focused on antipsychotic free acute schizophrenic patients, and the NMDA-enhancing agents has been shown to be beneficial in Alzheimer disease, posttraumatic stress disorder, autism and phobias. (page 18 second column lines 20-24., 24-28, 30-34). No mention or reference is given for unipolar or major depressive disorder non-psychotic, non-treatment resistant. In fact at the very last sentence Tsai in this December 2008 psychiatric newspaper article enters into speculation expressing some uncertainty that the NMDA-enhancing agents may be beneficial for innovative applications of other potential targets for those with other neuropsychiatric conditions. Depression is not mentioned. (Tsai GE. A new class of antipsychotic drugs: enhancing neurotransmission mediated by NMDA receptors) Psychiatric Times December 2008, 16-18.)

Therefore, this document does not foresee our claims, (it is not enabling, has insufficient disclosure; it fails to put the subject matter of our claims within the possession of the public, that is someone with general skills in the field could have not used the referenced document with their own knowledge to make our claimed invention themselves; so it does not affect the novelty of our application.

Baker et al, US 6,100,256 Use of NK-1 receptors antagonists for treating schizophrenic disorders. (Filed June 1998).

All of the claims in the Baker document are concerning the treatment or prevention of schizophrenia and not the subject of our claims.

In the Baker document their combination of NK-1 antagonist in combination with other antipsychotic agents *for the treatment of schizophrenic disorders* cannot foresee our claims (e.g., antipsychotic-antidepressant combination for treatment of a patient suffering form major depressive disorder [MDD](non-psychotic, non-treatment resistant); or for a patient having cognitive distortions with functional impairments; to give our combination for the prevention of suicide for patients suffering from [MDD](non-psychotic, non-treatment resistant), to give our combination as an initial treatment; or to giving our combination for protecting or remedying the development of tolerance toward the antidepressant, to avoid the paradoxical effect of an antidepressant to sensitize patients to depression; to give our combination for smoking cessation or nicotine withdrawal).

Therefore, this document does not foresee our claims, (it is not enabling, has insufficient disclosure; it fails to put the subject matter of our claims within the possession of the public, that is someone with general skills in the field could have not used the referenced document with their own knowledge to make our claimed invention themselves; so it does not affect the novelty of our Application. (We will also approach the question of novelty from other aspects later).

Our Application differs significantly from the referenced documents in the International Search Report to meet the Novelty test. Specifically, our method is different (e.g., suggesting an initial treatment) from theirs; the combination of drugs are different (antipsychotic-antidepressant), and it describes a new use.

To be lacking novelty all of the characteristics would had needed to be listed in a single prior art document. (See David Pressman Patent it yourself, Nolo 2004, p.5/15)

The combined teaching of the cited references still fail to fully teach the invention recited herein. (See James Rogers The Complete Patent Book, Sphinx Publishing 2003 p 222.)

The **Smith** article is worth a mentioning as an augmentation strategy of fluoxetine that could reduce the risk of suicide. (Smith WT et al. Short term augmentation of fluoxetine with clonazepam in the treatment of depression: A double-blind study. Am J Psychiatry 155:10 1998 1339-45.)

General patent principles

General patent principles the applicant relied on in crafting this reply, and additional considerations and general rules applied in the reply to MPTO:

The following was shown to the examiner so that he would better understand the applicant's point of views for his reasoning, and thus avoiding any miscommunications, and allowing the examiner to better explain any differences in the regulations if there is any. The following is the understanding of the applicant on some general US regulations: -

A) Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.**
If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

As we have shown the prior arts cited do not anticipate our claims.
We have also shown the secondary factors that the prior art teaches away.

B) If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

C) The PTO need to present a convincing line of reasoning for obviousness or the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

In other words the same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J).) "that references must ... suggest [our] claimed invention, or [the] examiner must present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references.
(Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." We have shown in our reply that there is no obviousness the prior art is different or not enabled, and the skilled in the art could not have disregarded the boundaries of standard of care without adequate guidance, and without going through a risk/benefit/side effect, available alternatives analysis (etc).
We came up with new inventive steps that enabled to use our invention.

D) The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combination therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224).

E) In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Another line of reasoning would also show of why the artisans and the authors of (all of) the cited prior art (patent) documents were not in the possession of our invention:

1) All these cited prior art (patent) documents were from big pharma and they would have the financial interest to pursue as many coverage (including our new use) would they been in the possession of our invention. If they were, they would have also no problem of providing the same disclosure and guidance that we did. They failed to do so. Therefore the big pharma prior art or the average skilled in the art was not in the possession of our invention and could not have followed the PTO's line of argument that was not convincing also for the reasons mentioned above.

2) The third requirement of the USC Title 35, Sec 112 (1) is the best mode requirement, which does not permit inventors to disclose only what they know to be their second best embodiment. In other words if they would have known a preferred way of using their invention they couldn't conceal this from the public. (The complete patent book page 25). Giving an extremely wide diagnostic category would be therefore in conflict of the patentability for that reason, would these documents really imply any other use that was already known in the art.

3) Giving an extremely wide diagnostic category [depression or all of the mental illnesses] (specifically **when enablement are very different for some of the subcategories** requiring additional (and non-disclosed **steps** by these prior art documents) would also show that the prior art (and the artisan) was not aware for that use. They could not have substituted these prior art documents for the purposes of our claims. The enablement are very different for some of the subcategories (like non-TRD and non-psychotic depression or as initial treatment for substantially all of said patients) requiring additional (and non-disclosed steps by these prior art documents).

4) The same applies to the low dose concept: Giving an extremely wide dose range as "preferred" application cannot be explained by the PTO as a low dose, or the low dose concept, especially when we have pointed out that Tollefson for olanzapine included a preferred **dose range which is 33% larger than the highest PDR approved dose**. This cannot include the low dose concept –as we defined – of usually being $1/3^{rd}$ of the dose given for psychosis! Tollefson (or the prior art)'s best mode therefore was not disclosed in sufficient detail to allow one skilled in the art to practice it (Fonar Corp. v. General Electric Co., 107 F.3d 1543 [Fed. Cir. 1997]. The complete patent book page 25.) As we also pointed out the Tollefson (and prior art) reference(s) are for a different use (and or patient population). In addition as we have discussed at page 12-13 [under 10d)] high doses of the

atypical medication have an – treatment emergent side effect – which is opposite of the intended use described in our claims.

As stated above the following two specifically applies to all of the prior art:
Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 220 also states, that: "The prior art reference … must teach or suggest all [our] claim limitations." **As we have shown it previously (including the secondary factors) that this is also not the case.**
and
In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Enablement and guidance for clarity

Since our application two publications appeared in professional publications both showing the efficacy of augmenting the newer antidepressants with an atypical antipsychotic medication wherein the method was effective for the treatment of suicidal ideations in all of the patients in the case report, and the double blind placebo controlled study also confirming significantly reducing suicidal ideation compared with the antidepressant group.

Viner WM. Et al Low dose risperidone augmentation of antidepressants in non-psychotic depressive disorders with suicidal ideation. Journal of Clinical Psychopharmacology Vol. 23(1) February 2003.

Reeves H et al, Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychiatry 69:8 2008 1228-1236.

However, please note that in both of these studies the patients had TRD. (Table 1 at page 105 in Viner, and page 1229 second column lines p13-16 in Reeves article. This is still a progress toward the direction of finally making a shift in the direction of or toward to the use of our method.

Our enablement

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion**." And "patent protection is granted in return for an **enabling disclosure of an invention**, not for vague intimations of general ideas that may or may not be workable."

We agree of the above, that a patent is a **compensation for its successful conclusion,** -and we have provided a successful conclusion that others (like the FDA directors) has failed to realize even in the intense media attention on the topic of our invention. (see secondry factors) As regards to patent protection is granted in return for an **enabling disclosure of an invention,** we could not agree more.

Please note that the current Government sponsored study (CATIE) to compare atypical antipsychotics with one single typical antipsychotic cost $40 Million, [and the data may be useless due to poor design] which is out of the scope of this independent inventor. (Please also note that Einstein's theory of relativity was proven with the development of atomic clocks well after his death and – would his invention otherwise be patentable – no-one argues that would have deserved a patent.) We brought this up in "as if" scenario and this is relevant in showing that sometimes breakthrough approaches cannot yet be proved by experiments. The expenses for research studies are out of the limit of this small entity inventor. Similar examples could be brought up for inventions on a new space shuttle to Mars or to a different galaxy. While nobody would have the time – in patent terms – to wait for an experiment to reach another galaxy, and provide the experimental "proofs" for the patent office, a small entity inventor or even many nations would not have the assets to experimentally prove and finance such a mission. The enablement would not have to be based on experiments, but on whether or not the inventor provided logical steps not recognized by others, and whether or not the inventor had given adequate guidance to enable the skilled in the art to practice the invention without expensive experimental data! (We have also shown in the referenced prior arts that the researches of the drug companies are often limited to a

small portion of the subject while they are using language to allow – without an analysis – for broad and unrelated claims that the experiments did not prove.) So enablement relying on vast number of resources can at times be far better then some ill designed limited experiments.

The applicant has other responsibilities to win bread for a living, and does not have an asset to that degree to sponsor studies. However, all these may be beside the point. We have shown that the invention can be used off label, without undue experimentation, without such large studies. We have also shown that the skilled in the art does not have to get all his questions answered, but to enable him for the use of the invention (for which no more scrutiny than for a drug company should be expected). If for any reason a drug company would want to use this invention for the purpose of getting FDA approval, (and with that as a fringe benefit) getting an extension for that drug company's existing patent, than necessary large studies can be performed as much as that is required for such a purpose. However, to enable the skilled in the art to practice the invention, we had fulfilled the requirement giving adequate guidance for being enabling. This enablement was completed by reintroducing (pasting) material from our provisional application.

Specifics on enablement:

We have been ample of giving guidance to enable the use of our invention. In our provisional application (re-entered herein) we have given a theory; or better yet reasons of why the (atypical) antipsychotic medications (either alone or in combination with antidepressants) may target and be useful for the treatment and prevention of depression and suicide. These reasons were based on our synthesis of multiple source of information and on our conclusions that others failed to make. We have included these for our reply in Appendix A, and B, below:

Appendix A

Our synthesis of multiple source of information and our conclusion was leading to explanation of how the antipsychotics (antidepressant-antipsychotic combination) may work and target the treatment and the prevention of depression and suicide. It should also be noted that the following conclusions were missed by the artisans of our specialty:

Depression is diagnosed according to DSM based on limited symptoms in addition to depressed mood – as also recited at page 11 of our utility. However, this practice leads our teaching not being recognized.

It is of note that DSM is still useful as the language of the skilled in the art to communicate; but is should not be called as (Diagnostic and Statistical Manual – DSM) but a differential diagnostic manual, as in our view this is what it is useful for. (In other words, by the symptoms what DSM describes, we can differentiate MDD from bipolar disorder for example, but the DSM symptom criterion list is not fully sufficient for diagnosing the depression for severity, or for residual symptoms, as it does not include and recognize many "other" depressive symptoms that we feel should be included.)

In the provisional application (and being also subject of a separate invention [11/034,447]) we were showing that multitudes of other psychiatric symptoms should be included when we test, diagnose and treat depression. {Please see re-entered (bulleted) part from the provisional application). That

shows that the antipsychotics would target many "extended" depressive symptoms that are non-DSM, and that are not recognized as part of the depressive symptom list. The bulleted parts starting from the second one deserve particular attention for our explanation.

So, as we have shown in the provisional (and below) that if the (atypical) antipsychotics target these "other" symptoms that we as psychiatrists do not rely on in diagnosing, testing and treating depression; then the **sum of combining these factors would point out that indeed the antipsychotics are useful in treating depression. That would point out that the antipsychotics (antidepressant-antipsychotic combination) should be used for the purpose of our claims.** With this we support (and show how the antipsychotics are working). [In our provisional we have shown that 1) we should use these antipsychotics for the purpose provided, and 2) should be relying on these "other" depressive symptoms not within the DSM criterion list. The combination of factors mentioned in this paragraph includes that in addition of the direct effect of the antipsychotics on these non-recognised "depressive symptoms", there is an indirect effects of the antipsychotics ("pseudo placebo effect") as well: it has an additional positive psychological effect on the depressed individual, as lifting of one depressive symptom contributes to the lifting of the other by the overall improvement of the patient and by lifting hopelessness. On the other hand the psychological factors are also interacting with morphological neuronal changes – as we have shown in the provisional application and as discussed under "clinical neuroplasticity" in Appendix B;].

Our guidance, no matter how convincing or "obvious" it sounds now – it was not recognized by prior art at the time of our invention. [In fact our guidance in about 4 - 6 years later is still not being recognized, despite all of the intense media and FDA attention on this subject].

See parts under "**Amendment to Specification"** from boxed part of PTO page 23, 0203 – page 31 till 0226 boxed part ending with "as adjunct to the antidepressants." --- the part ending until the start of boxed part :"PTO page 17, 0177 till page 18 end of 0178".

It is extremely important to emphasize, that our synthesis of data, and the conclusions that we have drawn were missed by the skilled in the art.

Appendix B

We will discuss here the interaction between the psychological, medication and neuronal changes [and even between genetic expressions]. (We also need referring back to the above Appendix A, where we already discussed interaction between psychological effects and medication effects.) **No claims in this application had been drawn regarding Appendix B**, but it relates to our guidance. Since we had even detailed in our provisional such an innovative synthesis between the psychological, medication effects and the neuronal changes, therefore we revisited this issue here.

In the provisional application (being also subject of a separate invention [11/034,447]) we have discussed research on neuroplasticity (the adaptation of the brain to change) in other areas than depression, followed by our synthesis of how that knowledge can be used in education on treatment of depression.

*In the stroke victims the **strong (not paralyzed) hand** needs to be **"immobilized"** with placing a large mitts on it, so that the patient cannot use it and be **forced to use the week hand** (the paralyzed*

hand) with which he or she is instructed to ***turn dominos over and practice that*** *for six hours a day.* ***Change in corresponding neuronal connections*** *results in regaining the lost function.*

Therefore, we came up with the "domino" metaphor as an analogy taken from the rehabilitation of the stroke victims and that metaphor to be used in the rehabilitation of the depressed.

The ***strong negativistic (pessimistic) thinking****, with the global thinking, jumping to conclusions, cognitive distortions needs to be* ***"immobilized"*** *so that the depressed person's* ***"weak positive thinking pattern"*** *and the corresponding neuronal connections (through neuroplasticity) could be mobilized, and* ***strengthened with practice,*** *so that the normal, non-depressed function would be regained. This strengthening can be achieved through many ways, 1) through teaching cognitive therapy (catching and modifying [negative] automatic thinking, using cognitive analysis; 2) changing the situation and with this changing the predominant thought content; 3) using therapy to change the meaning attributed; and 4) using medications (or other means) that "helps either immobilizing the negative thinking and cognitive distortions, or doing so by relieving the symptoms of depression" or "strengthening or facilitating the neuronal growth in the neuroplasticity model to facilitate the recovery".*

The opposite is true for this neuroplasticity change if we are forced to practice a negative thinking pattern. That would result in depression. The "Stanford prison experiment" if analyzed retrospectively, it proves that harmful effect. We gave examples to this in the provisional as well:

See "Amendment to Specification", the pertaining parts re-entered from the provisional applications are *starting with* the *paragraph:*

"Looking beyond the changes in the hippocampus and receptor level in depressed patients, it would be worthwhile to separate the term synaptic plasticity from neuronal plasticity."

until

"In summary for this section in looking the global picture, that is the role of neuronal plasticity in depression, the psychological and biological explanations indeed do blend together."

Additional notes on enabling:

While **all of the above had shown, that we had put our method in the possession of the skilled in the art (psychiatrist), and that we have done that without the need of undue experimentation,** the following can be specifically revisited:

In re Wands, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The above had shown, that:

Regarding (2) the state of the prior art; sufficient evidence was provided, that one skilled in the art at the time we filed the application would have not come up with the same invention as we did. The teaching away despite of intense media and FDA attention also provides evidence to that fact. However, with off label use, and with the guidance given by us one skilled in the art would be able to practice the invention without undue experimentation.

(4) the predictability or unpredictability of the art: we can say, that with the guidance given by us one skilled in the art would have been able to practice the invention without undue experimentation. Our guidance have strongly shifted the art toward predictability.

(6) the amount of direction or guidance presented: As shown above we have provided an extensive, and sufficient amount of direction or guidance so that someone can practice our invention without undue experimentation. We have discussed risk/benefit alternatives, and reasons to use our method for the prevention of suicide (also taking into account the benefit of the group). We were teaching exactly (within reason) of how to make use of our invention for the various purpose provided. We were also providing hypothetical examples. In addition the skilled in the art knows of how one can use already FDA approved medications off label. Therefore no undue experimentation would be necessary.

(8) the quantity of experimentation necessary: No undue amount of experimentation is necessary, as we have extensively shown in our reply.

Therefore our invention is enabling, does not require undue experimentation.

Consider the lives saved compared to the worst infectious epidemic of all times

Reeves study showed a total of 42% decrease of suicidal scores in the combination treatment about double then those that continued on antidepressant only (and placebo).
Over 26 years since it was known that antipsychotics are antagonists for 5HT2 (see reference under Pivac above). That translates with the 30.000 suicide per year in the US alone of saving 327.000 lives (out of the 780.000). This difference since that time of not saving these lives by not using our method is more than the casualties of the worst infectious epidemics of all times the 1918 flue epidemic. Since the time of our application till now, in about six and a half years till the Reeves study came our at the end of 2008 the lives not saved by not using our method (and in our inability to convince the drug companies to take steps) is up to 81.200 lives.
If it would have been obvious from the prior art – if the PTO as an official governmental body and by definition an expert with the role of determining obviousness would determine so against my arguments – then this would become the worst scandal of our century and a huge liability for many entities for not doing anything about this for over 26 years.

We respectfully request the allowance of our amended claims.

Amendments to the claims:

This listing of claims will replace all prior versions, and listings, or claims in the application:

Listing of Claims

1. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

2. (Previously presented): A method for treatment of a patient suffering from unipolar depression, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism,

an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

3. (Previously presented): A method for treatment of a non-psychotic patient having cognitive distortions with functional impairment or health hazards, wherein said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, and wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

4. (Original): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is an atypical antipsychotic.

5. (Original): The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, and pharmaceutically acceptable salts thereof.

6. (Previously presented): The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

7. (Original): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is a dopamine system stabilizer.

8. (Original): The method of Claim 7, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

9. (Previously presented): The method of Claims 1, 2, or 3, wherein said antipsychotic drug is selected from the group consisting of perphenazine, trifluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride, and wherein said antipsychotic is administered at a low dose.

10. (Previously presented): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

11. (Original): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with

serotonin/norepinephrine/dopamine reuptake inhibition and an antidepressant with norepinephrine and dopamine reuptake inhibition.

12. (Previously presented): The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan.

13. (Original): The method of Claims 1, 2, or 3, wherein said antidepressant is a selective serotonin reuptake inhibitor.

14. (Previously presented): The method of Claim 11, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

15. (Previously presented): The method of Claim 11, wherein said antidepressant is clomipramine.

16. (Previously presented): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is risperidone.

17. (Previously presented): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is quetiapine.

18. (Previously presented): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is olanzapine.

19. (Previously presented): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is aripiprazole.

20. (Previously presented): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is risperidone.

21. (Previously presented): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is quetiapine.

22. (Previously presented): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is olanzapine.

23. (Previously presented): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is aripiprazole.

24. (Previously presented): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is risperidone.

25. (Previously presented): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is quetiapine.

26. (Previously presented): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is olanzapine.

27. (Previously presented): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is aripiprazole.

28. (Previously presented): The method of Claim10, wherein said antidepressant is fluvoxamine and said antipsychotic is risperidone.

29. (Previously presented): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is quetiapine.

30. (Previously presented): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is olanzapine.

31. (Previously presented): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is aripiprazole.

32. (Previously presented): The method of Claim 10, wherein said antidepressant is fluoxetine and said antipsychotic is ziprasidone.

33. (Previously presented): The method of Claim 10, wherein said antidepressant is paroxetine and said antipsychotic is ziprasidone.

34. (Previously presented): The method of Claim 10, wherein said antidepressant is sertraline and said antipsychotic is ziprasidone.

35. (Previously presented): The method of Claim 10, wherein said antidepressant is fluvoxamine and said antipsychotic is ziprasidone.

36. (Previously presented): The method of Claim 10, wherein said antipsychotic is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

37. (Previously presented): The method of Claims 1, 2, or 3, wherein an effective amount of said antidepressant is its recommended therapeutic dose, or its effective starting dose.

38. (Original): The method of Claims 1, 2, or 3, wherein the administration is oral.

39. (Cancelled)

40. (Cancelled)

41. (Previously presented): The method of Claims 1 or 2, wherein said treatment is given for resisting suicide.

42. (Previously presented): The method of Claim 2, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, -providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said depression.

43. (Previously presented): The method of Claim 3, wherein said treatment is given at a time selected from the group consisting of, as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for resisting suicide.

44. (Cancelled)

45. (Cancelled)

46. (Cancelled)

47. (Cancelled)

48. (Previously presented): The method of Claim 1, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, -providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said depression.

49. (Previously presented): The method of Claim 3, wherein said treatment is given as an initial treatment, for a patient suffering from major depressive disorder, and for resisting suicide, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

50. (Original): The method of Claim 3, wherein treatment is given for smoking cessation or nicotine withdrawal.

51. (Previously presented): The method of Claim 13, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, zimelidine, indalpine, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

52. (Previously presented): The method of Claim 13, wherein said antidepressant is clomipramine, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

53. (Currently amended): The method of Claim 2, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, inhibiting worsening of said depression from said antidepressant, and treating worsening of said depression from said antidepressant~~,~~.

54. (Previously presented): The method of Claim 49, wherein said treatment is effected for at least one of the group consisting of inhibiting disease progression, modifying the course of said major depressive disorder, inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, providing a neuroprotective effect, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said major depressive disorder, avoiding worsening of said major depressive disorder, from said antidepressant, treating worsening of said major depressive disorder from said antidepressant, and treating residual symptoms of said major depressive disorder.

55. (Previously presented): The method of Claim 1 wherein said treatment is effected for treating substantially all of said patients treated by said physician or other health care provider by said method, wherein said treatment is given for resisting suicide.

56. (Previously presented): The method of Claim 1 including treating a plurality of said patients by said method, wherein said antipsychotic drug is administered at a low dose, and said treatment is given for resisting suicide.

57. (Previously presented): The method of Claim 2 wherein said treatment is effected for treating substantially all of said patients treated by said physician or other health care provider by said method, and wherein said treatment is given for resisting suicide.

58. (Previously presented): The method of Claim 2 including treating a plurality of said patients by said method, wherein said antipsychotic drug is administered at a low dose, and said treatment is given for resisting suicide.

59. (Previously presented): The method of Claims 1, 2, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

60. (Previously presented): The method of Claims 55, 56, 57, or 58 wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

61. (Previously presented): The method of Claim 3, wherein said treatment is given for resisting suicide.

62. (Previously presented): The method of Claim 3, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group.

63. (Previously presented): The method of Claims 55, 57 or 61, wherein said antipsychotic drug is an atypical antipsychotic.

64. (Previously presented): The method of Claims 55, 57 or 61, wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, and pharmaceutically acceptable salts thereof.

65. (Previously presented): The method of Claims 1, 2, 55, 57 or 61, wherein said antipsychotic is the active metabolite of risperidone.

66. (Previously presented): The method of Claims 55, 57 or 61, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

67. (Previously presented): The method of Claims 55, 57 or 61, wherein said antipsychotic drug is a dopamine system stabilizer.

68. (Previously presented): The method of 55, 57 or 61, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

69. (Previously presented): The method of 55, 57 or 61, wherein said antipsychotic drug is selected from the group consisting of perphenazine, trifluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride.

70. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition and an antidepressant with norepinephrine and dopamine reuptake inhibition.

71. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2

antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan.

72. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is a selective serotonin reuptake inhibitor.

73. (Previously presented): The method of 55, 57 or 61, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

74. (Previously presented): The method of 55, 57 or 61, wherein said antidepressant is clomipramine.

75. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is risperidone.

76. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is quetiapine.

77. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is olanzapine.

78. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is aripiprazole.

79. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is risperidone.

80. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is quetiapine.

81. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is olanzapine.

82. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is aripiprazole.

83. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is risperidone.

84. (Currently amended):~~)~~: The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is quetiapine.

85. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is olanzapine.

86. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is aripiprazole.

87. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is risperidone.

88. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is quetiapine.

89. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is olanzapine.

90. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is aripiprazole.

91. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluoxetine and said antipsychotic is ziprasidone.

92. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is paroxetine and said antipsychotic is ziprasidone.

93. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is sertraline and said antipsychotic is ziprasidone.

94. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is fluvoxamine and said antipsychotic is ziprasidone.

95. (Previously presented): The method of Claims 55, 57 or 61, wherein said antipsychotic is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

96. (Previously presented): The method of Claims 55, 57 or 61, wherein an effective amount of said antidepressant is its recommended therapeutic dose, or its effective starting dose.

97. (Previously presented): The method of Claims 55, 57 or 61, wherein the administration is oral.

98. (Previously presented): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

99. (Previously presented): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of protecting against the development of tolerance toward the antidepressant; and remedying the development of tolerance toward said antidepressant.

100. (Previously presented): The method of Claims 55, 57, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant

sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

101. (Previously presented): The method of Claims 55, 57 or 61, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

102. (Previously presented): The method of Claims 55, 57 or 61, wherein said treatment is given for providing a neuroprotective effect.

103. (Previously presented): The method of Claims 55, 57 or 61, wherein said treatment is given for treating residual symptoms of said depression.

104. (Previously presented – for the reply to the 3rd OA): The method of Claims 55, 57 or 61, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

105. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is clomipramine.

106. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine.

107. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine, and wherein said antipsychotic are selected from the group consisting of perphenazine, tripfluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride.

108. (Previously presented): The method of Claims 55, 57 or 61, wherein said antidepressant is ketamine, and wherein said antipsychotic are selected from the group consisting of risperidone, quetiapine, olanzapine, ziprazidone, and aripriprazole, and the effective amount per day is from 0.5mg to 4 mg for risperidone, from 25mg to 400 mg for quetiapine, from 2.5mg to 10 mg for olanzapine, from 10-40mg for ziprazidone, and 2.5mg to 15mg for aripriprazole.

109. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

110. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the

group consisting of delaying relapse; resisting relapse; and resisting the recurrence of said depression.

111. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of protecting against development of tolerance toward said antidepressant; and remedying the development of tolerance toward said antidepressant.

112. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of protecting against development of tolerance toward said antidepressant; and remedying the development of tolerance toward said antidepressant.

113. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an

antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

114. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression; for avoiding worsening of said depression from said antidepressant; and treating worsening of said depression from said antidepressant.

115. (Previously presented): a method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said

antidepressant sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

116. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; avoiding a paradoxical effect of said antidepressant -sensitizing said patients to said depression and causing suicidal ideation; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicide; treating a paradoxical effect of said antidepressant sensitizing said patients to said depression and causing suicidal ideation; avoiding worsening of said depression from said antidepressant and causing suicide; avoiding worsening of said depression from said antidepressant and causing suicidal ideation; treating worsening of said depression from said antidepressant and causing suicide; and treating worsening of said depression from said antidepressant and causing suicidal ideation.

117. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone,

femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said major depressive disorder categorized as non-treatment resistant and non-psychotic, and wherein said treatment is given for treating residual symptoms of said depression.

118. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, said unipolar depression categorized as non-treatment resistant and non-psychotic; and wherein said treatment is given for treating residual symptoms of depression.

119. (Previously presented): A method for treatment of a patient suffering from unipolar depression, said method comprising administering to said patient an effective amount of an antipsychotic drug wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, wherein said treatment is effected for resisting suicide, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

120. (Previously presented): The method of Claim 119, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of antidepressant sensitizing patients to depression; treating a paradoxical effect of antidepressant sensitizing patients to depression; for avoiding worsening of depression from the antidepressant; and treating worsening of depression from the antidepressant.

121. (Previously presented): The method of Claim 119, wherein said treatment is effected at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon

presentation of said patient to a physician or other health care provider, and wherein said atypical antipsychotic drug or said dopamine system stabilizer is administered at a low dose.

122. (Previously presented): The method of Claims 119, 120, 121, wherein said atypical antipsychotic or said dopamine system stabilizer is selected from the group consisting of risperidone, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from 0.5mg to 4mg for risperidone, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

123. (Previously presented): The method of Claims 119, 120, 121, wherein said atypical antipsychotic is quetiapene, and the effective amount per day is from 25mg to 400mg.

124. (Previously presented): The method of Claim 10, wherein said treatment is selected as the first choice of treatment, and said treatment is effected for resisting suicide.

125. (Previously presented): The method of Claim 49, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, and wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole.

126. (Previously presented): A method for treatment of a patient having cognitive distortions with functional impairment or health hazards, wherein said patient is suffering from major depressive disorder, wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic, wherein said method comprising administering to said patient an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and

antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor_potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

127 (Previously presented): A method for treatment of a patient having cognitive distortions with functional impairment or health hazards, wherein said patient is suffering from major depressive disorder, wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic, wherein the method comprising administering to said patient an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer and wherein said treatment is effected for resisting suicide.

128 (Previously presented): The method of Claim 127, wherein said treatment is effected for at least one of the group consisting of avoiding a paradoxical effect of antidepressant sensitizing patients to depression; treating a paradoxical effect of antidepressant sensitizing patients to depression; for avoiding worsening of depression from the antidepressant; and treating worsening of depression from the antidepressant.

129. (Previously presented): The method of Claim 127, wherein said treatment is effected at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider, and wherein said atypical antipsychotic drug or said dopamine system stabilizer is administered at a low dose.

130. (Currently amended): The method of Claims 126, 127, 128, 130, wherein said atypical antipsychotic or said dopamine system stabilizer is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone and aripiprazole, and the effective amount per day is from

0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

131. (Previously presented): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase and wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites, wherein said antidepressant is used in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

132. (Previously presented): A method for treatment of a patient suffering from unipolar depression, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase and wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites and wherein said antidepressant is used in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

133. (Previously presented): A method for treatment of a non-psychotic patient having cognitive distortions with functional impairment or health hazards, wherein said method comprising

administering to said patient an effective amount of an antidepressant, wherein said antidepressant is an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase, wherein said antidepressant is selected from an antidepressant with final common pathway of antidepressant action associated with the NMDA receptor complex, inducing adaptive changes in the glycine regulatory sites of the NMDA receptor producing a 2-4 fold reduction in the glycine GLY to inhibit 5,7-DCKA binding to the NMDA receptor-associated glycine sites, wherein said antidepressant is used in combination with an antipsychotic drug, and wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer.

134. (Previously presented): The method of Claims 131-133, wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, olanzapine, iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof.

135. (Previously presented): The method of Claims 131-133, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.

136. (Previously presented): The method of Claims Claims 131-132, wherein said treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant, and treating residual symptoms of said depression.

137. (Previously presented): The method of Claims 131-132, wherein said treatment is given for resisting suicide.

138. (Previously presented): The method of Claims 131-132, wherein said treatment is effected for treating substantially all of said patients treated by said physician or said other health care provider by said method, and wherein said treatment is given for resisting suicide.

139. (Previously presented): The method of Claims 131-132, wherein said treatment is given for resisting suicide, and wherein said treatment is given for the benefit of the group of said patients being treated by said physician or health care provider.

140. (Currently amended): The method of Claims 1-2, or 131-132, wherein a physician or other health care provider is involving said patient in the decision-making of said method by discussing with said patient the *risks/benefits,* side effects of the medications, ~~as said physician or said other health care provider is supposed to discussing with said patient the risks/benefits, side effects of the medications, and available alternatives anyway, and since predicting which patients will commit suicide is an impossible task,~~ wherein discussion of why we cannot continue to refrain using ~~*the*~~ said method is selected from the group comprising at least one of the following steps (a) wherein a said physician or said other health care provider is taking into account the risk/benefit for a group not just for an individual for said combination use of said antidepressants and said antipsychotics, (b) wherein a said physician or said other health care provider in further support of said decision-making of said method is drawing examples for said step (a) selected from the group consisting of (b-1) ~~from consisting~~ of how said healthcare providers were treating appendicitis, (b-2) how said healthcare providers are following similar procedures when giving thiamin routinely for everybody in the emergency room before giving intravenous glucose therefore preventing Korsakoff's syndrome in alcoholics, and (b-3) how said healthcare providers are routinely testing for drug screen in the emergency room even when the patient says that he or she is absolutely not taking any illicit drugs, therefore said examples (a, b-1, b-2 and b-3) are ~~in order to~~ pointing out that said taking into account the risk/benefit for a group not just for an individual is customary in the medical practice, is a standard procedure and good clinical practice, thus needs to be applied for said method, (c) wherein in this step a said physician or said other health care provider is pointing out that in starting treatment right away with said combination use of said antidepressants and said antipsychotics ~~right away~~ in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor, (d) and wherein in this step it is discussed that in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer said atypical antipsychotics when in a separate diagnostic category from major depressive disorder, in borderline personality disorder said physicians were not afraid of using the combination of antidepressants with antipsychotic medications and when in comparison, said major depressive

disorder has two to two and a half times more risk for committed suicide ~~*two to two and a half times more risk for committed suicide*~~.

141. (Currently amended): ~~(New claim)~~ The method of Claim 140, wherein a said physician or said other health care provider is discussing with said patient other added benefits from the said combination use of said antidepressants and said antipsychotics wherein said added benefits of said treatment is effected for at least one of the group consisting of inhibiting disease progression, modifying the course of said major depressive disorder, inhibiting the development of tolerance toward said antidepressant, remedying the development of tolerance toward said antidepressant, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said major depressive disorder, avoiding worsening of said major depressive disorder from said antidepressant, treating worsening of said major depressive disorder from said antidepressant.

142. (Currently amended): The method of Claims1-2, or 131-132, wherein the said method is used ~~ful~~ for the purposes selected from the group consisting of (a) resisting nonadherence to the prescribed medication, (b) resisting said patients discontinuing, said prescribed medication.

143. (Currently amended): The method of Claim 140, wherein a said physician or said other health care provider is discussing with said patient other reasons and other rationales for using the combination of said antidepressant and said antipsychotic medications in said major depression, wherein said other reasons and other rationales
are selected from ~~is effected for~~ at least one of the group consisting of ~~discussion of~~ the following steps (a) retrospective analysis of suicide committers with major depression showed that many of them have received inadequate treatment (b) it had been shown that among the depressed patients who committed suicide many of them actually had psychotic depression that went unrecognized so they were not receiving antipsychotic medications, (c) cognitive distortions like jumping into conclusions without the analysis of the facts that is prematurely getting into conclusions are characteristic for depression and that it seems that there is an overlap between the cognitive distortions, the mini psychosis of borderline personality disorder, and the full blown psychosis of psychotics, all of them being out of touch with reality but in different degrees and that atypical antipsychotics may be useful for targeting the cognitive distortions that overlap with psychosis (d) and wherein in that step the role of cognitive distortions in hopelessness and suicide is discussed, as a study confirmed the predictive value of hopelessness in suicide, and that hopelessness is the

greatest predictor of suicide risk beyond the first year, however suicide occurs in only five per cent of terminally ill patients and their greatest risk factor is untreated depression, therefore it is not hopelessness per se, but its perception, that is the cognitive distortion characteristic of depression, that seems to be the most important factor, and since for strong perceptual disturbances, said physicians had been using said antipsychotics, the adjunctive use of said antipsychotics with said antidepressants in the treatment of said major depressive disorders is supported.

144. (New): The method of Claims140 and 143, wherein the said method is used for the purposes selected from the group consisting of (a) resisting nonadherence to the prescribed medication, (b) resisting said patients discontinuing, said prescribed medication.

145. (New): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is a newer antidepressant, and wherein said newer antidepressant is defined as an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase in combination with an antipsychotic drug, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

146. (New): The method of Claims 145, wherein said antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic and a dopamine system stabilizer,
wherein said atypical antipsychotic drug is selected from the group consisting of risperidone, quetiapene, olanzapine, ziprasidone iloperidone, melperone, amperozide, and pharmaceutically acceptable salts thereof, and wherein said dopamine system stabilizer is aripiprazole.

147. (New): A method for treatment of a non-psychotic and non-depressed patient selected from the group consisting of (a) a patient having cognitive distortions with functional impairment or health hazards and (b) of a patient undergoing smoking cessation or nicotine withdrawal, wherein

in either case (a) or (b) the method is comprising of administering to said non-psychotic and non-depressed patient an effective amount of a newer antidepressant, wherein said newer antidepressant is defined excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic and a dopamine system stabilizer, wherein said antipsychotic drug is administered at a low dose, and wherein said treatment is given for resisting suicide.

SUMMARY AND CONCLUSIONS

In view of the foregoing, it is respectfully submitted that the amended claims are supported by an enabling disclosure and are patentable over the applied art. As a result, it is respectfully submitted that Claims 1-38, 41-43 and 48-143 and new Claims 144-147 are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

If for any reason you would feel that any of the claims as amended would not be allowed, please schedule a meeting with the Applicant.

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Please note, that the Applicant have lost his attorney representation, and is relying on your guidance.

Respectfully submitted,

Peter Migaly, M.D.